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ANAPHYLAXIS AND SENSITISATION

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ANAPHYLAXIS AND SENSITISATION

With Special Reference to the Skin and its Diseases

BY

R. CRANSTON LOW, M.D., F.R.C.P.

LECTURER ON DISEASES OF THE SKIN
EDINBURGH UNIVERSITY

AND

ASSISTANT PHYSICIAN FOR DISEASES OF THE SKIN
THE ROYAL INFIRMARY
EDINBURGH

WITH 16 COLOURED PLATES AND 7 HALF-TONE ILLUSTRATIONS

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TO

MY WIFE

PREFACE

This volume is a reproduction of a thesis which was presented for the degree of M.D. of the University of Edinburgh and awarded a gold medal.

I wish to express my thanks to my Alma Mater for permission to publish it.

The work was carried out in the Skin Department of the Royal Infirmary, and I am indebted to Sir Norman Walker for the very liberal way in which the material in his department has been put at my disposal.

The preparation of the fungus extracts, etc., was carried out in the Laboratory of the Royal College of Physicians.

It is hoped that the work will be of assistance to the pathologist and bacteriologist as well as to the dermatologist.

The literature on the subject is enormous, but, so far as possible, reference has been made to all the important articles, a full list of which is given at the end.

I have tried to be impartial in drawing conclusions. In many cases the facts, as they are known, are recorded, and the reader is left to form his own opinion. The subject of sensitisation is especially important in the study of the diseases of the skin, because a better knowledge of the method of production of an eruption must necessarily lead to better and more rational methods of treatment. Hitherto the tendency in many cases has been to treat the skin lesion itself, rather than the cause which underlies it. No attempt has been made to describe the actual skin eruptions, as this volume deals entirely with the method of their production.

My grateful thanks are due to Sir Norman Walker for the use of the coloured plates which have appeared or will appear in his *Introduction to Dermatology*.

I am also indebted to the Librarian of the Royal College of Physicians and his Assistant for the great assistance which they have given me in connection with the literature of the subject.

EDINBURGH, *July* 1924.

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ANAPHYLAXIS AND SENSITISATION

WITH SPECIAL REFERENCE TO THE SKIN AND ITS DISEASES

CHAPTER I

INTRODUCTION

The aim of this volume is to describe and discuss the phenomena of Anaphylaxis and Sensitisation in so far as they affect the skin. Before taking up each section separately, it will be well to give a short general description of our present knowledge of these phenomena and an explanation of the numerous terms which will be used throughout this work.

Anaphylaxis was the term introduced by **Richet** to describe the series of phenomena which occur on reinjection into animals, after an interval of several days, of certain substances which were harmless on first injection. As the animal had been rendered more susceptible to the substance injected, **Richet** thought the condition was the opposite of Prophylaxis or Immunity, and gave it the name Anaphylaxis.

THE PHENOMENA OF ANAPHYLAXIS

As animals such as the guinea-pig give much more intense reactions than human beings, it is best to study the phenomena of anaphylaxis in them. Horse serum can be injected in fairly large doses into guinea-pigs without producing any symptoms. When, however, a small dose of horse serum is injected subcutaneously, intraperitoneally, or intravenously into a guinea-pig, and 10 days later a second injection is given, the animal develops symptoms of distress and usually dies within an hour or so. A

few minutes after the second injection the animal becomes restless, shows symptoms of difficulty in breathing, and urine and fæces are usually discharged. This stage of excitement is rapidly followed by one of paresis, the animal falling on its side and the limbs jerking. The convulsions continue with increasing paralysis and the animal dies from asphyxia. If the animal be not very susceptible the symptoms may be delayed in their appearance, and in these cases the animal may recover. These are the symptoms of anaphylactic shock. If the animal recovers, for some days afterwards (at least 10–12 days), it is found to be in a state of Anergy, *i.e.* the opposite of Allergy or sensitisation. During this stage of Anergy, large doses of the sensitising agent can be injected with impunity, and in this way the animal can be permanently immunised.

INCUBATION PERIOD AND DURATION OF SENSITISATION

For 8–10 days after the sensitising injection subsequent injection of the sensitising substance produces no signs of anaphylaxis. If a second injection is given during the incubation period the animal will probably become immune rather than hypersensitive. **Rosenau** and **Anderson** found that the degree of hypersensitiveness increases from the 10th to the 21st day, after which it gradually diminishes somewhat. They showed that the animal may still be sensitive 1096 days later and that the sensitiveness probably lasts all the life of the animal. This corresponds with what is known to occur in man in bacterial sensitisation. Persons who have once had a tuberculous infection will always give a positive skin Pirquet reaction for the rest of their lives.

The amount of serum necessary to sensitise a guinea-pig is astonishingly small. **Rosenau** and **Anderson** found that 0·000,001 c.c. might be sufficient to cause sensitisation, but the initial dose given is usually 0·001 c.c. Larger doses of serum will also sensitise, but the incubation period is longer. To obtain a fatal result the second or toxogenic dose must be considerably larger than the minimum sensitising dose.

Pfeiffer has shown that during anaphylactic shock the

temperature falls. **Biedl** and **Kraus, Friedberger** and **Arthus** also showed that there is a diminished coagulability of the blood. Leucopenia and diminution of complement are also found. Post-mortem the most striking change is a permanent distension of the lungs resembling emphysema. This was described by **Gay** and **Southard** and later by **Auer** and **Lewis** and confirmed by **Anderson** and **Schultz.** The alveoli of the lung are distended, and rupture of the walls sometimes occurs. The bronchioles are contracted, and death results from asphyxiation, the heart continuing to beat after respiration has ceased. The lung changes are extraordinarily like those seen in human beings with asthma.

Rabbits can be sensitised similarly to guinea-pigs, but not so easily. The symptoms differ in some respects from those in guinea-pigs. Dogs may also be sensitised, but the reaction is not so violent and death not so frequent. Many other animals, such as cats, horses, sheep, etc., have been used, and although the symptoms vary somewhat according to the species, on the whole, the reactions are similar.

ANAPHYLAXIS IN MAN

Some have expressed doubt as to whether the reactions seen in man after second injections of a foreign serum are truly anaphylactic, but taking into consideration the differences which exist between the anaphylactic reactions in different species of animals it is not to be wondered at that the reactions in human beings differ considerably from those seen in the guinea-pig, rabbit, etc. The reactions in man will be discussed later under Serum Disease.

As it is now known that Anaphylaxis and Immunity are very closely linked, many consider the term a bad one and prefer to use that of Supersensitiveness, Hypersensitiveness, or Sensitisation. **Pirquet** also introduced the term Allergy, which means an altered reactivity. The substance which causes anaphylaxis is called an anaphylactogen, sensitiser, or allergen according to **Pirquet.**

So far as we know at present only proteins are capable of acting as anaphylactogens. These proteins may be derived from animal tissues, such as blood serum, milk, etc., vegetable

and plant tissues, and bacterial substances. Several workers have claimed to have produced anaphylaxis with non-protein substances such as lipoids, but **Ritchie** and **Miller, White** and others have shown that, when the lipoids are pure, anaphylaxis cannot be produced. It is, however, possible that non-protein substances may combine with protein in the tissues, and so cause anaphylaxis. In this way certain reactions, such as those produced by drugs like salvarsan, may be explained.

The purer a protein the more readily it acts as a sensitiser. There seems to be still some doubt as to whether the whole protein molecule or only a part of it is required to produce sensitisation. All proteins produce anaphylaxis most readily when in solution, because they are then more easily absorbed into the body-cells.

METHODS OF SENSITISATION

The anaphylactogen may be introduced into man by injection as in treatment with sera. Absorption through the skin by rubbing may also cause sensitisation. It will be shown later that rubbing the juice of the primula plant into the skin can cause sensitisation. Absorption may also occur through the intestine. Guinea-pigs may be sensitised by feeding them on serum and meat, as was proved by **Rosenau** and **Anderson.** In this way human beings often become sensitised to such foods as eggs, shell-fish, pork, etc. Further reference to this intestinal absorption of proteins will be made later when discussing eczema and urticaria in children.

Rosenau succeeded, by keeping guinea-pigs in stables with horses, in sensitising them to horse serum. This explains the method by which asthmatic persons may become sensitive to horse serum without previously being actually injected with it. The emanations from the horse may be absorbed by inhalation, but there is also always the possibility of their getting into the mouth and being swallowed. This may occur by inhalation through the mouth or contamination of food with the hands or clothes which have been in contact with horses. **Rosenau** and **Amos** showed that the exhaled breath of men when condensed and injected into guinea-pigs could sensitise them to injections of human serum.

CHRONIC ANAPHYLAXIS

It has been shown by **Boughton** that, if repeated anaphylactic shock is induced in guinea-pigs by injections of egg white and beef serum, these animals show lesions of the smaller arteries of the kidneys, liver, spleen, and heart, characterised by degeneration and regeneration of the endothelium, œdema and fissuring of the intima and media, and sometimes splitting of the internal elastic lamina. These lesions are not found in the larger arteries, capillaries, and veins. Perivascular infiltration is also present in many cases. The changes in the arterioles lead to corresponding degenerations in the kidney tissue. These changes are similar to the chronic degenerative changes seen in man in the so-called toxæmias and autointoxications.

PREVENTION OF ANAPHYLACTIC SHOCK

I. Desensitisation, Antianaphylaxis, or Anergy

As already stated, if an animal recovers from anaphylactic shock it is found to be in a state of desensitisation, antianaphylaxis, or anergy, and further doses of the sensitising agent can be injected with impunity. This refractory period lasts at least 10–12 days, but may continue for several weeks. After the refractory period is past the animal again becomes hypersensitive, but usually not to the same degree as before. **Otto, Rosenau** and **Anderson,** and **Besredka** and **Steinhardt** showed that sensitised animals can be rendered refractory or antianaphylactic by the administration of small doses of the protein used to sensitise. The doses must be too small to cause any symptoms. It is possible by repeated small doses so to desensitise an animal that it will withstand doses many times larger than the one necessary to cause fatal anaphylaxis in a sensitive animal which has not been so treated. Intravenous injection causes desensitisation in a few minutes; intraperitoneal in a few hours; and subcutaneous injection may take 24 hours to produce an effect. This method of desensitisation has been used to prevent anaphylactic shock in human beings who are being treated with serum injections. **Besredka** recommends that the quantity to be given

be split up into fractional doses which are injected every 10–20 minutes, gradually increasing the amounts, till the full dose has been given. A prophylactic injection of the serum can also be given per rectum and the real therapeutic dose later on.

Lewis also found that desensitisation could be accomplished in animals by the slow intravenous injection of the sensitising substance. By means of the Woodyat pump minute measured doses of the serum may be injected very slowly at measured intervals of time. **Coca** also found this method of desensitisation to be effective. **Marbe** and **Rachewski** also used a modification of the above method. They gave a preliminary cutaneous inoculation of the serum, which in about $1\frac{1}{2}$–2 hours protected the animal so that a full dose could be given with safety. They found that this cutaneous inoculation only protected the animal for 48 hours, and after that time the animal was even more hypersensitive than it was previously. For the condition of protection induced by this preliminary cutaneous inoculation they propose the name "l'état phylactique," and for the subsequent heightened hypersensitiveness "l'état ana-anaphylactique."

Desensitisation may also be accomplished by feeding a sensitive individual on increasing quantities of the substance which produces the symptoms. **Park** quotes such a case of an infant which was breast-fed. This child was given a little cow's milk at the age of six weeks, and 3–4 hours later vomited, became collapsed, and suffered from diarrhœa. No such symptoms occurred after drinking goat's milk. This child was desensitised by feeding on increasing quantities of cow's milk, beginning with 0·0001 c.c. well diluted. At first very slight symptoms were produced, but these gradually disappeared. The dose was gradually increased according to the symptoms till the child could take large quantities of cow's milk daily with impunity. This method of desensitisation by feeding will be again referred to under food sensitisations.

Wells and **Osborne** found that by feeding animals for a long time with oats they became antianaphylactic, so that no satisfactory anaphylactic reaction could be obtained by two properly spaced injections. Therefore, feeding animals for a short time on foreign proteins, especially animal proteins, will sensitise

them to these proteins, whereas feeding them for longer periods will desensitise them.

It is to be noted that the state of antianaphylaxis or desensitisation is not the same as immunity. It is not permanent as the animal later goes back to the sensitive condition again.

II. Other Means of Preventing Anaphylaxis

Brodin, Richet, and **St Girons** found by experiments on dogs that the intravenous injection of *Sodium chloride* counteracts anaphylaxis when given in doses of not less than 0·8 grm. per kilo weight.

Friedberger and **Hartoch** also obtained the same results in guinea-pigs by injection of hypertonic salt solution. **Dale,** who also worked at this subject, thinks that the salt acts by diminishing the irritability of the smooth muscles of the body, which by their contraction are responsible for many of the symptoms of anaphylactic shock.

Friedberger and **Hartoch's** results were later confirmed by **Zinnser, Lieb,** and **Dwyer.**

Similarly, **Sicard** and **Parof** found that 10–15 grm. of *Sod. bicarb.* by the mouth 15 minutes beforehand, or 0·5–2 grm. *Sod. carbonate* intravenously, will ward off anaphylactic shock.

Besredka also showed that *Calcium chloride,* when injected the day before the intoxicating dose, prevents anaphylactic shock. This is interesting because calcium chloride has long been given for the treatment of urticaria.

Sodium hyposulphite was also found by **Lumière** and **Chevrotin** to prevent anaphylaxis if added in small amount to the serum before injection.

Adrenalin, too, has a remarkable effect in preventing or relieving anaphylactic shock. **Pelz** and **Jackson** found that it prevented anaphylactic shock in dogs. It has also been used with success in asthma, serum sickness, and urticaria.

Atropin was found by **Auer** and **Lewis** to prevent shock in guinea-pigs. *Belladonna* is used extensively in the treatment of asthma.

Chloral hydrate was found by **Richet, Banzhof** and **Steinhardt,** and **Banzhof** and **Famulener** to prevent shock in animals. The

animal must be deeply under the hypnotic. **John Thomson** also found chloral hydrate useful in treating infants suffering from a certain type of convulsions which he considers of anaphylactic origin.

Anæsthetising a sensitised animal can prevent symptoms of shock. Chloroform, ether, and similar drugs have been used. Whether this is simply due to the paralysis of the nervous system and consequent prevention of symptoms or not is doubtful. **Bronfenbrenner** and **Schlesinger** found that certain anæsthetics increase the antitryptic action of the blood, and therefore they argue that that is sufficient to stop the activity of the proteolytic enzyme which they consider necessary for the production of the shock. **Besredka** found that preparations of opium and morphine had no effect in preventing anaphylactic shock.

Quite recently **Duprez** showed that it is possible to prevent anaphylactic shock in the guinea-pig by the previous injection of a lipoidal emulsion. The mechanism of this result has not yet been worked out.

PASSIVE ANAPHYLAXIS

It has been shown by **Gay** and **Southard, Richet, Otto,** and others that the serum of a hypersensitive animal, when injected into a normal animal, will render the latter hypersensitive; therefore passive anaphylaxis can be produced. Passive anaphylaxis can be produced by transference of serum to an animal of the same species (homologous), or to an animal of another species (heterologous). Passive anaphylaxis takes some time to develop. By intravenous injection of the serum it takes about 4 hours till the animal is anaphylactic; by intraperitoneal injection about 24 hours; and by subcutaneous injection 24–48 hours are necessary. Passive anaphylaxis lasts for some days or weeks, but is never so permanent as active anaphylaxis. In addition to serum from a hypersensitive animal, the serum of an animal in the incubation stage before sensitisation can be demonstrated can also produce passive anaphylaxis. Likewise injection of serum from an antianaphylactic animal and immune serum are able to produce it.

Anderson, Schenk, and others have shown that the young of

sensitised female guinea-pigs are sensitive. This is an example of homologous passive anaphylaxis. **Schenk** also claims that it can be transmitted through the sperm of sensitised males.

SPECIFICITY OF ANAPHYLAXIS

The anaphylactic reaction is to a high degree specific. Group reactions, however, occur. An animal sensitive to sheep serum will react, but less violently, to goat serum. Similarly, animals sensitised to human serum will react to the sera of the higher apes.

Rosenau and **Anderson** found that guinea-pigs sensitised to human milk or dog's milk did not react to cow's milk, but that animals sensitised to sheep's milk might give a definite reaction to cow's milk. This indicates that when the milk is from an animal of a closely allied species heterologous reactions are apt to occur.

Wells and **Osborne** have also seen the same group reactions in anaphylaxis due to vegetable proteins. Pure *Hordein* from barley will produce an anaphylactic reaction in a guinea-pig sensitised to pure *Gliadin* of wheat. There seems to be some chemical reactive group common to both these substances. Anaphylaxis therefore shows a species specificity. An animal cannot be sensitised to its own tissues. The only exception to this seems to be the crystalline lens of the eye. **Uhlenhuth** and **Haendel** showed that animals can be sensitised to their own lens protein. **Wells** showed that, although there is a species specificity, there is also a specificity by which it is possible to distinguish proteins in the same substance. **Wells** was able by the anaphylactic reactions to distinguish four proteins in the white of the hen's egg, viz. ovomucoid, crystallised egg albumin, globulin, and ovovitellin. This is an example of a chemical specificity which is independent of the species specificity.

As with animal and vegetable proteins, so with bacterial proteins group reactions may occur. **Holobut** found that specific reactions could be obtained with B. Typhosus and B. Coli. But interaction between the two organisms could also occur. Other observers, however, maintain that bacterial anaphylaxis is absolutely specific for each organism.

THEORIES AS TO THE MECHANISM OF ANAPHYLAXIS

Many theories have been put forward to explain the mechanism of Anaphylaxis. None, however, give an absolutely satisfactory explanation of all the phenomena. As true anaphylaxis is due to a protein, this protein, when injected, acts as an antigen, *i.e.* a substance which leads to the formation of antibodies. There are produced also under certain conditions precipitins, agglutinins, lysins, and complement fixing bodies. These are intimately connected with the changes in anaphylaxis.

One of the chief points of controversy is, as to whether or not a poisonous substance is produced in the reaction. If some poison is produced, it has to be decided whether this poison is produced in the cells of the body (cellular theory) or in the circulating fluids (humoral theory). If no poison is produced, then the symptoms may be due to some disturbance of the balance of the colloids or enzymes in the circulating fluids (physical theory).

As many workers have used different terms for substances concerned in the reactions, I think it will conduce to clearness if a short summary is given of the views of those who have done most work on the subject, and if, after that, the cellular, humoral, and physical theories are discussed.

Richet suggested that when the sensitiser or anaphylactogen is first injected it causes the production of a substance which he called Toxogenin. This toxogenin, on the second injection of the protein, combines with the protein to produce a poison called Apotoxin, which through its action on the nervous system causes the symptoms of anaphylaxis. It will be seen later that **Richet's** Apotoxin is practically **Friedberger's** Anaphylatoxin under another name. In the latter's theory toxogenin corresponds to antibody and complement.

Gay and **Southard** think that every antigen consists of two elements, one toxic (anaphylactin) and the other non-toxic or sensitising. On the first injection the toxic anaphylactin is eliminated from the body and the non-toxic sensitising element is retained in the body-cells. When a second injection is given

the toxic anaphylactin in the reinjected protein is rapidly absorbed by the sensitised cells and anaphylactic shock results.

Besredka also assumes that there are two distinct elements in the antigen, viz. sensibilisogen and antisensibilisin. On the first injection the sensibilisogen causes the development of an antibody which he calls sensibilisin, and the antisensibilisin is excreted or destroyed by the animal. On the second injection the antisensibilisin element in the antigen combines with the sensibilisin and produces a toxic substance which causes the symptoms of anaphylaxis.

Nicolle thinks that anaphylaxis is due to two substances, viz. Albuminolysin and Albuminocoagulin. Sensitisation produces a large amount of the former and a smaller amount of the latter in the tissues. The second dose of antigen is rapidly lysed by the albuminolysin with the formation of toxic substances.

Friedberger explains anaphylaxis on the basis of **Ehrlich's** side-chain theory of immunity. The foreign protein calls forth the production of side-chains which unite with and neutralise the antigen. **Friedberger** assumes that these side-chains or receptors remain sessile in the cells. When antigen is reinjected for the second time it combines in the presence of antibody with complement to produce a toxic substance called Anaphylatoxin, which produces the symptoms. This theory explains the absence of complement in anaphylactic shock. After sensitisation the cells of the body contain sessile receptors which have a great affinity for the antigen.

Vaughan and **Wheeler** think that when a protein antigen is injected, the tissues produce a specific ferment which digests it and splits up the protein. By boiling proteins with an alcoholic solution of sodium hydrate they split up the protein into a non-toxic alcohol-soluble part and a toxic alcohol-insoluble part. The toxic part, when injected into normal guinea-pigs, caused death with all the symptoms of anaphylactic shock. This toxic part of the protein can be obtained from all proteins and seems to be identical in all, hence the uniformity of symptoms in anaphylactic shock in the same animal whatever the protein used to produce the shock. The specificity of the reaction is due to the non-toxic part of the protein, which varies in each case. **Vaughan** and **Wheeler** think " that protein susceptibility

and immunity are different manifestations of the same process. Both depend on the development of a specific proteolytic ferment. When the specific ferment splits up a living foreign proteid (such as a bacterium) before it has time to multiply, we say that the animal is immune. When the cleavage action is less prompt, but sufficiently so to split up the living proteid before it elaborates a fatal amount of the poison, the animal sickens but recovers. When the action of the ferment is still less prompt and the living proteid constructs enough poison to kill, then its liberation causes death. This specific proteolytic ferment is stored up in the cells of the animal as a result of the first injection, and remains as a zymogen until activated by the second injection of the same proteid. We regard the production of the specific zymogen not as the formation of a new body, but as resulting from an alteration in the atomic arrangement within the proteid molecule and a consequent change in its chemism."

There is some doubt as to where the protein which produces the poison is derived from. **Jobling** and **Petersen, Bronfenbrenner** and others hold that it comes from the animal's own serum. **Doerr** thinks it is derived from the serum by the absorption of the inhibitory antibodies. **Vaughan, Friedberger,** and others think that it comes from the injected protein.

In support of the cleavage of protein is the further evidence of the reactions which can be produced with substances such as peptone, agar, etc. **Biedl** and **Kraus** showed that the injection of peptone produces symptoms in the dog similar to anaphylaxis. This was confirmed by **Karsner** in the guinea-pig. The symptoms and post-mortem findings are the same as those produced by anaphylatoxin. **Bordet** and **Besredka** and **Strobel** found that agar treated with serum produces similar anaphylactoid phenomena. Similarly, **Keysser** and **Wassermann** found that barium sulphate and kaolin, when mixed with complement, produced a substance with similar action to anaphylatoxin. **Novy** and **De Kruif** also obtained like results with serum peptone and serum agar. **Kopaczewski** found that anaphylactic shock could be produced by the contact of serum with pectin, which is a non-nitrogenous colloid substance. **Bordet** showed the same to hold good for pararobin, **Friedberger** and **Tsuneoki** for kaolin, **Schmidt** and **Nathan** for starch, and **Kritchewsky** for the sap of a coty-

ledon plant. Histamin, which is an amin produced by splitting off carbon dioxide from histidin by chemical agencies, can also, when injected, produce symptoms like anaphylactic shock.

All these reactions with substances which contain no nitrogen help to support the view that anaphylactic shock is due to the cleavage of protein by specific ferments with the production of a toxic substance.

The work of **Doerr, Jobling,** and **Petersen** and others tends to show that neither specific antigen nor complement are necessary for the production of the anaphylactic reaction. Similarly, the presence of antibody is not essential as the anaphylactic poison can be produced in vitro. An animal in a state of antianaphylaxis to a given antigen is not protected from the effect of anaphylatoxin.

It must, however, be pointed out that although many hold that the symptoms produced by these non-nitrogenous substances are almost identical with those of true anaphylaxis, there are others who think that the reaction should be called anaphylactoid and separated from true anaphylaxis. But all will admit that the reactions are similar and related in some way.

CELLULAR AND HUMORAL THEORIES OF ANAPHYLAXIS

A great deal has been written on the question of whether the anaphylactic reaction occurs in the blood stream, *i.e.* between antibodies or other substances in the serum and the antigen, or in the cells between the sessile antibodies and the antigen. The fact that passive anaphylaxis can be produced shows that the blood of the sensitised animal contains some substance which can be transferred from one animal to another. As already seen, various names have been given to it. **Richet** speaks of Toxogenin, **Besredka** of Sensibilisin, **Nicolle** of Albuminolysin, and **Pirquet** of Allergin. Many object to the use of the term antibody for this substance. If used in the sense that it is protective, antibody is not a good name. However, it is a convenient term to use for want of a better.

Precipitins and agglutinins occur in the anaphylactic condition, but most workers are agreed that they play a secondary rôle in

the process. The supporters of the humoral theory assume that the Toxogenin, Sensibilisin, Albuminolysin, or Allergin is a specific lytic amboceptor which by union with complement forms a ferment capable of splitting the protein molecule so as to produce a toxic substance capable of producing the symptoms of anaphylaxis.

Friedberger's theory of sessile receptors in the cells with a great affinity for antigen assumes that the cells play the chief part in the reaction. **Vaughan** and **Wheeler's** split-protein theory also assumes the storing-up of the specific proteolytic ferment by the cells.

A great deal of experimental work has been done by **Weil, Coca, Schultz, Dale,** and others by isolating the various organs of sensitised animals and perfusing them or applying to them the specific antigen in order to see whether these organs react to the poison or whether the poison can be extracted from them. **Weil** was particularly emphatic that cellular antibody alone was responsible for the reaction of acute anaphylactic shock. The humoral theory is committed to the belief that the circulating antibody may exercise a protective (immunity) or an injurious (anaphylaxis) function depending on various accidental circumstances. **Weil** thought that the cellular theory explained the relation of anaphylaxis and immunity better than any other, the circulating antibody being essentially protective as in immunity and the cellular antibody always the agent of anaphylactic symptoms.

Weil showed that in dogs it is the liver cell which is sensitised, and all the features of anaphylactic shock in that animal appear to be due to the effect of the antigen on the sensitised liver.

The symptoms of anaphylaxis are due to the contraction of the smooth muscles of the body, *e.g.* the emptying of the bladder and bowel and the difficulty in breathing and death from spasm of the bronchioles. **Schultz** isolated the smooth muscle of sensitised guinea-pig's intestine, uterus, bladder, aorta, and vena cava, freed them from blood, and suspended them in **Ringer's** solution. He applied various sera to them. They contracted when normal serum was applied, but to a very much more marked degree when the horse serum to which the animal had been sensitised was applied. Objection has been made to the above type of experi-

ment on the ground that the reaction is not purely cellular as some blood is always left in the tissues. **Larson** and **Bell** showed that it is impossible to wash all the blood out of an organ by perfusion methods. The efferent fluid becomes free from blood and albumin in a short time, but these substances reappear if the perfusion is suspended for a few minutes. By perfusing organs with **Locke's** fluid containing Indian ink the course taken by the fluid through the organ has been mapped out, and it has been found that a surprisingly small part of the capillary system is really washed out by the perfusing fluid. Therefore they conclude that this type of experiment does not remove circulating antibodies completely, and therefore does not establish the presence of cellular antibodies. **Coca,** on the contrary, holds that perfusion experiments are valid. He experimented with living sensitised guinea-pigs. He removed the blood, but only so much as to leave less than a single minimal sensitising quantity, and then introduced Indian ink in saline solution into the circulation. The animal was killed 2 minutes later, and the liver, lungs, etc., showed an even distribution of ink particles all through the organs. Therefore he quotes perfusion experiments as uncontrovertible evidence of the cellular site of anaphylaxis.

Pearse and **Eisenbray** replaced the blood of a normal dog with that of a sensitised animal, and also conversely replaced the blood of a sensitised dog by that of a normal dog. Each dog was then given an intoxicating dose of the sensitising antigen, and symptoms were produced in the sensitised dog with normal blood, but no symptoms occurred in the normal dog with sensitised blood. Therefore they hold that the reaction was a cellular and not a blood reaction. **Coca** confirmed these experiments with the guinea-pig.

Manwaring, Kusama, and **Crowe** did a large number of experiments by perfusing the liver and lungs of sensitised and normal animals, and they showed that the perfusion of sensitised lungs with antigenic serum causes them to respond with bronchiole constriction such as occurs in anaphylactic shock. From these and other experiments by **Simonds** and others there is evidence to show that in anaphylaxis the toxic substances are produced in the liver and act on the lung.

Dale also did perfusion experiments with isolated uterine

muscle of guinea-pigs, and claims to have proved "beyond reasonable doubt the intrinsic hypersensitiveness of that tissue to the specific antigen."

Experiments on passive anaphylaxis also support the cellular theory. A certain interval of time is necessary after the transference of blood before the animal becomes sensitised. **Weil** has also shown that the simultaneous injection of antigen and the blood of a sensitised animal fails to produce anaphylaxis. During the interval of time the cells anchor or produce the sensitising substance, and only after that has occurred is the animal passively sensitised. On the humoral theory the incubation period necessary for passive anaphylaxis cannot be explained.

From the foregoing discussion, therefore, we must conclude that the bulk of the evidence goes to support the cellular theory of anaphylaxis. But, as **Bordet** said in a recent lecture on the subject in Edinburgh, probably both the cells and circulating fluid play a part. The blood certainly is required to convey the antigens and antibodies to or from the cells, and therefore the two elements must be intimately concerned in the reactions.

PHYSICAL THEORIES OF ANAPHYLAXIS

Doerr commits himself to an exclusively physical theory. He thinks that the blood contains preformed toxic substances such as are produced when the blood clots. These toxic substances are held in abeyance by "hindering bodies" in the complement. When the hindering bodies are removed or absorbed on the second injection, the colloid equilibrium of the serum is disturbed and the toxic substances in the complement are liberated to produce anaphylactic symptoms. **Doerr** considers that this theory explains the reactions due to certain colloids such as pectin, etc.

Jobling and **Petersen** also hold that anaphylaxis is due to an alteration in colloids. They think that the serum proteins are normally protected from digestion intravitally by the presence of protective lipoids (unsaturated fatty acids), *i.e.* antiferments or antitrypsin. Partial removal of these antiferments by adsorbants like agar, bacteria, etc. allows the proteolytic ferments in the serum to split the proteins and proteoses into toxic products (so-called anaphylatoxins).

Dold and **Bronfenbrenner** also agree with the above views that anaphylaxis is due to the removal of the antitrypsin from the serum so that a poison is produced by autodigestion of the serum. **Dale** also thinks that anaphylaxis is due to a change in the dispersion of the protoplasmic colloids.

The reactions produced by **Kopaczewski** with pectin, **Bordet** with agar and such like non-nitrogenous substances, tend to support the physical theory of colloid dispersion.

As already mentioned, however, there is still some doubt as to whether the reactions produced by these substances are truly anaphylactic. **Novy** and **De Kruif** strongly maintain that these reactions to peptone, agar, etc., are examples of true anaphylaxis. Others prefer to separate them, and refer to the reactions as peptone shock, colloid shock, and anaphylactoid shock.

THE NERVOUS SYSTEM AND ANAPHYLAXIS

That the nervous system is concerned in the production of anaphylactic symptoms is probable. The fact that anæsthetics prevent anaphylactic shock taking place supports this view, but as already mentioned **Bronfenbrenner** and **Schlesinger** found that certain anæsthetics increase the antitryptic action of the blood, and they consider that it is for that reason that anaphylaxis does not occur. Application of antigen to isolated organs of a sensitised animal to produce contraction of the unstriped muscle of the organ gives no assistance as the nerve endings are still present.

Arnold and **Leschke** think that the effects of anaphylaxis are produced through the nervous system, because, although the anaphylactic poison causes contraction of the muscles of the bronchi, bowel, uterus, etc., it also causes dilatation of the muscular coats of the vessels. They therefore think the symptoms of anaphylaxis can be explained by the exciting effect of the anaphylactic poison in the endings of the parasympathetic system in the smooth muscles.

The antagonistic effect of atropin (which paralyses the vagus endings) in retarding anaphylaxis supports this contention. **Sheurer** and **Strasman** have shown that section of both vagi does not prevent the spasm of the bronchial muscles in anaphy-

laxis, so that if the reaction occurs through the nerves it must do so in the nerve endings in the muscle. **Pottenger** came to the conclusion that in toxæmias the disturbances of visceral function are produced through irritation of the vegetative nervous system, while the anaphylactic syndrome is due to a general stimulation of the vagus. In support of this, **Eppinger** and **Hess** showed that vagotonic persons react very readily and strongly after sensitisation to foreign protein. Intracutaneous reinjection of serum produced in such persons not only a local reaction but also a general urticaria.

Czerny also, in grouping children under different diatheses, referred to what he called the exudative diathesis and showed that children of that diathesis have a mild type of thymus activity with parasympathetic irritation. This expresses itself as eczema, urticaria, and asthma. These children have a "hair-trigger" sympathetic nervous system in which the vagus is so irritable that explosive symptoms are readily produced by foreign proteins. As the vegetative nervous system is closely linked with the endocrine glands, **Czerny** also thinks that in all children of the lymphatic diathesis there is an underlying want of balance of the secretions of the ductless glands. As will be shown later, certain persons can be much more readily sensitised than others, and heredity plays an important part in asthma, eczema, etc. Probably the essential factor for successful sensitisation is the possession of such a diathesis as **Czerny** described.

Further investigation, however, is necessary before any definite conclusions can be drawn as to the part played by the nervous system.

THE DUCTLESS GLANDS IN ANAPHYLAXIS

The ductless glands, such as the thyroid and suprarenals, may play a part in the reactions of anaphylaxis, but it is doubtful whether they are affected by the reaction products or through the action of these products on the nervous system. As already stated, the administration of adrenalin can prevent anaphylactic shock in animals. It is also known to be of great use in the treatment of asthma, serum sickness, and urticaria. In surgical shock with lowered blood pressure **Bedford** found that the

epinephrine content of the suprarenal blood was greatly increased, and this, he thinks, is a reaction to prevent dilatation of the vessels and lowering of the blood pressure. **Smith** and **Ravitz** examined the epinephrine content of the suprarenals in sensitised and shocked animals and found it to be the same as in normal control animals.

There is therefore no definite evidence of any change in the suprarenal secretion in anaphylaxis.

Thyroid has been used with benefit in asthma. It may act by stimulating the suprarenal secretion, and **Graham Brown** ascribes the beneficial effect of iodides in asthma to the same cause.

By examining the blood sugar in thyroid diseases **Janney** and **Isaacson** found that thyroid disease favours protein catabolism, thus linking the thyroid to anaphylaxis, in which there is marked evidence of protein catabolism.

Kepinow and **Metalnikow** published some recent work on the relation of the thyroid gland to tuberculin sensitisation in infected animals. In one series of experiments they found that in guinea-pigs from which the thyroids had been removed, and which were subsequently infected with tubercle, an injection of tuberculin produced practically no general reaction, whereas in control animals with thyroids a marked general reaction occurred. They also found that passive sensitisation to tubercle could be induced with the serum of tuberculous guinea-pigs, but not with the serum of tuberculous thyroidectomised animals. **Kepinow** also found that in animals from which the thyroid had been removed the injection of the toxogenic dose after previous sensitisation failed to cause anaphylactic shock. **Appelmans,** on the contrary, obtained exactly opposite results. He found that anaphylactic shock occurred in guinea-pigs sensitised to serum, whether their thyroids had been removed or not.

Further work is necessary, however, before the part played by the ductless glands in anaphylaxis can be estimated.

CHANGES IN THE BLOOD IN ANAPHYLAXIS IN RELATION TO THE SKIN

A discussion of the biochemical changes in the blood, such as the formation of precipitins, agglutinins, complement fixing

bodies, is outside the scope of this work. Reference has already been made to the diminution of the coagulability of the blood in anaphylactic shock as demonstrated by **Biedl** and **Kraus, Arthus, Friedberger,** and **Weiss** and **Tsuru. Witzinger,** in studying the effect of foreign serum injections in man on the coagulability of the blood, found that the first sensitising injection was regularly followed by an acceleration of coagulation, which subsided in 24 hours. From the 7th to the 10th day after injection a second acceleration of coagulation occurred. The reinjection of serum, however (*i.e.* the intoxicating dose), was followed in 5 or 6 hours by a marked retardation of coagulation.

Extraordinarily little attention seems to have been paid to the coagulability of the blood in skin diseases, but in some cases of chronic urticaria, a disease which will be seen later to be anaphylactic in nature, a diminished coagulability of the blood has been noted. Leucopenia in anaphylaxis has also been referred to. This change does not seem to be common in skin conditions, the reverse condition being more likely to occur. The fact that the skin is so exposed to secondary infections with pus-producing organisms of all kinds would vitiate any results which might be obtained by blood examination in most skin diseases.

Eosinophilia, however, is a blood change which has a close association with anaphylaxis and with many skin conditions. **Stchastnyi** and **André** and **Courmont** demonstrated a considerable increase in the blood eosinophile cells after injection of hæmolytic sera. **Howard** found that injection of egg albumin into animals caused a blood eosinophilia. **Schlecht,** by repeated injections of foreign albumin into guinea-pigs, found that eosinophilia was produced both in the blood and locally in the peritoneum at the seat of injection. This eosinophilia begins after an incubation period of 4–8 days, which is associated with a hypo-eosinophilia. Negative results were obtained by injecting normal saline, Ringer's solution, nuclein, and vitellin. Positive results followed injection of serum albumin and globulin, egg white, and peptone. **Schlecht** thinks that the eosinophile cells may have a special function of absorbing albumin, and that their presence is a protective reaction on the part of the body. **Schlecht** and **Schwenker** also found that the bronchi and lungs of guinea-pigs in anaphylactic shock show a marked local eosinophilia, and **Schlecht**

showed in the local reaction produced at the seat of reinjection in a sensitised animal (**Arthus** phenomenon) that a marked collection of eosinophile cells occurred in the epithelium and corium of the skin. Adrenalin, which controls certain cases of asthma and urticaria, was also found to cause a diminution or complete disappearance of eosinophile cells from the circulation.

It was also shown by **Stchastnyi** that injection of alien red cells caused both a local and general eosinophilia.

Weinberg and **Seguin** likewise found that the toxogenic dose of antigen produced an eosinophilia which appeared 1–3 days later. They think this is due to a direct irritation of the hæmopoietic system by the antigen.

Herrick did a number of experiments on guinea-pigs by giving intraperitoneal injections of an aqueous extract of ascaris lumbricoides. This caused a marked eosinophilia of the blood. **Herrick** concludes that sensitisation of the animal is necessary before an eosinophilia can occur, because it is impossible to produce such eosinophilia when the animals are immune to the extract. He also states that the substance in the extract of the round worms which causes the sensitisation is a protein, and that previous sensitisation is necessary for the development of the eosinophilia.

The question is what exact relation a blood eosinophilia bears to sensitisation, and whether all diseases in which eosinophilia occurs are anaphylactic. **Cowie** and **Colhoun** go so far as to state that unless there is an eosinophilia, any given condition cannot be anaphylactic. I do not think, however, that there is sufficient evidence to support that view in every case. Eosinophilia is known to occur in asthma and hay fever, which are admittedly anaphylactic conditions. But it may also occur in spleno-medullary leucæmia, rheumatic fever, scarlet fever, typhoid fever, septicæmia, infection with intestinal parasites, some bone diseases, and malignant infections. It also occurs after malaria and pneumonia. Enough is not known about all these conditions from which to draw conclusions, but it is possible that all cause sensitisation to some protein, either bacterial or otherwise, and so lead to an eosinophilia.

Of the diseases of the skin the Pemphigus group (including dermatitis herpetiformis) is always associated with a marked

eosinophilia up to 40 or 50 per cent. Unfortunately, not much is known as to the cause of these conditions, but they are generally considered as intestinal toxæmias. This question will be discussed later under these diseases. In urticaria, which is undoubtedly a sensitisation condition, eosinophilia often occurs. It has also been recorded in eczema (especially if widespread), psoriasis, scleroderma, scabies, lepra, lupus (if extensive), pellagra, erythema multiforme, and impetigo contagiosa.

Straubli thinks that eosinophilia in skin diseases occurs as a result of disturbances of the intestinal tract in consequence of autointoxication as well as by absorption from the outside. That absorption of chemical substances may cause eosinophilia is shown by the fact that **Leredde** found an eosinophilia after ingestion of antipyrin, and **Bezancon** and **Labbé** after administration of potassium iodide. **Ewing** and **Da Costa** state that eosinophilia occurs after injection of tuberculin. **Berger** found that it occurred in infants after ingestion of foreign protein, because he found that infants previously fed exclusively on the breast almost regularly developed eosinophilia in 7–10 days following the administration of cow's milk.

Moschowitz is a strong upholder of the connection between anaphylaxis and eosinophilia. He thinks "that the invasion of eosinophiles in increased numbers into the organism is the expression of an active agent, or the agent itself in the production of anaphylaxis." He suggests that the relief of anaphylactic diseases might consist in the administration of agents known to cause a negative chemotaxis for eosinophiles, and states that injection of dead bacteria are known to act in this manner.

It is therefore evident that eosinophilia occurs in the blood in many conditions, especially of the skin, which are admittedly associated with sensitisation; but at present there is not sufficient evidence to show what the exact nature of the reaction is.

CHAPTER II

ANAPHYLAXIS IN MAN

SERUM SICKNESS

Serum sickness is now generally acknowledged to be a true anaphylactic phenomenon. It is the name applied first by **Pirquet** and **Schick** to the clinical symptoms which follow the injection of horse serum. The serum of other animals, *e.g.* the ox or rabbit, may also produce the same symptoms. Although most often due to the use of antitoxic sera for diphtheria or tetanus, the symptoms are caused by the horse serum and not by the antitoxine. The larger the dose of serum the more likely are symptoms to occur. **Ker** says, "we may expect to chiefly meet with them in mild and moderate cases (of diphtheria) which have received very liberal dosage."

The chief features of serum sickness are skin rashes, pyrexia, and joint pains, but œdema, especially of eyelids, and adenitis may occur. Vomiting may also occur, but is not very common. The most important symptom is the skin rash, which may assume various forms. *Urticarial* rashes are the most common. Typical urticarial wheals of large size and irregular shape appear usually near the site of injection first, but spread to other parts of the body and limbs. Itching may be intense. The rash may continue to come out for 2 or 3 days. The urticarial rash usually appears from the 8th to the 11th day after injection.

The rash may, however, be in the form of a multiform erythema with large bluish-red blotches or patches with circinate outline. Occasionally hæmorrhages and morbilliform and scarlatiniform rashes occur.

Kolmer states that in 1000 consecutive cases of diphtheria treated in the Philadelphia Hospital for Contagious Disease, a

rash developed in 43 per cent. Rashes may occur after a primary or after several injections. They are due to the foreign serum, when injected, calling forth the production of an antibody or ferment, which acts on the serum still in the circulation. This causes its cleavage and liberates a poison which causes the symptoms. It takes several days till this antibody is formed, and that is why the rash does not usually appear till the 8th to the 11th day. It has been shown by **Weil** that a foreign serum on injection remains in the circulation for many days. As soon as the antibody is formed in the circulation in sufficient amount, *i.e.* after 8–11 days, the symptoms appear. If the dose of serum is small, although the antibody is formed, there may not be any serum left in the circulation to cause symptoms. That is the reason why trouble is more likely to occur after large doses of serum than after small doses. If, on the other hand, a person has had an injection of serum some weeks or months previously, the reinjection is likely to be followed by an " immediate " reaction within 24–48 hours. The antibody is already there, and immediately reacts with the antigen. If the reinjection is made a year or more after the first injection, the symptoms usually appear in 4–7 days, *i.e.* an " accelerated " reaction. The explanation of this reaction is that although no antibody is present at the time of reinjection, the body cells having been previously stimulated to produce antibody, can do so more quickly, hence the accelerated reaction. But if a small amount of antibody is still present at the time of reinjection, one gets an " immediate " local reaction within 24–48 hours at the site of injection, followed in 4–7 days by a general " accelerated " reaction.

The immediate reaction described above therefore corresponds very closely to the milder forms of anaphylaxis as seen on laboratory animals. A sensitised animal, such as the rabbit, if it is subjected to an anaphylactic shock and recovers, frequently shows within the following days a very marked general urticarial rash with wheals and great itching, which leads to such vigorous scratching that the animal almost denudes itself of fur.

In human beings severe forms of serum disease, characterised by sudden onset within a few minutes after the injection, have been recorded. These cases show extreme prostration and dyspnœa, and may end fatally as in anaphylactic shock in

animals. These fatal cases are very rare considering the number of injections given. Asthmatics, who are sensitive to the horse, are particularly liable to this risk. **Sumner** reports such a case this year in a girl aged 8, who died within 5 minutes after a prophylactic injection of antidiphtheritic serum. **Dean** also recorded in 1922 a case of a soldier who died with cyanosis, vomiting, and collapse 70 minutes after the 4th injection of antitetanus serum. In this case a post-mortem was performed, and it was found that the liver had a deep purplish colour and seemed to contain an excess of blood. Microscopically, the liver showed extreme congestion with swelling of the liver cells, and in some cells a disappearance of the nucleus. The lungs showed an irregular dilatation of the capillaries with the alveoli dilated in some places and compressed in others. **Dean** points out the similarity between this anaphylactic shock in man and in the dog, and thinks that the chief and essential change is in the liver, and that the dilatation of the capillaries of that organ cause the fall in blood pressure. Somewhat similar cases have also been reported recently by **Pehu** and **Bertoye, Martin** and others. To show how small a dose can produce fatal results, a case of **Boughton's** may be quoted. A man, aged 29, who had suffered for 10–12 years from horse asthma, was given a dose of 1 minim of horse serum and died within 45 minutes. In this case all the gross and microscopical appearances at the post-mortem were like those of experimental anaphylaxis in animals.

Jousset and others, who have given large numbers of serum injections without producing any signs of anaphylaxis, hold that the risk of a fatal termination is nil, but in the face of the cases referred to above, there is no doubt that the risk does exist. Probably not more than 50 fatal cases have been recorded, but although that is a small percentage in the total number of cases treated, one must admit the possibility of grave danger.

THE PREVENTION OF SERUM DISEASE: DESENSITISATION

Before giving horse serum, especially in individuals in whom there is any suspicion that they may be sensitive either from

previous inoculation or from attacks of asthma, urticaria, etc., it is advisable to test the patient. The injection of a small dose to produce a general reaction is inadvisable in view of **Boughton's** fatal case after a dose of 1 minim, but by the application of the cutaneous test valuable information without risk may be obtained. The serum is applied to a small scarified area of skin, and within 15 minutes a wheal surrounded by an area of erythema appears. The intracutaneous test may also be used. These cutaneous tests will be referred to fully when the cutaneous reactions come to be discussed.

If the person to be inoculated is sensitive to horse serum, if possible ox serum should be used for the treatment, and it is a good plan to use ox antidiphtheritic serum for all prophylactic injections, so that if the person develops diphtheria at any time later, the horse antidiphtheritic serum can be used.

Even in cases where one has no reason to suspect a previous sensitisation, and the case is not urgent, it is advisable to give a preliminary injection of 0·5 c.c. of serum, followed in 3 or 4 hours by the therapeutic dose. Preliminary rectal injection of the serum, as recommended by **Besredka,** may also be used. **Mackenzie** recommends that in sensitive persons the first desensitising dose should be given subcutaneously, beginning with not more than 0·025 c.c. This dose should be doubled every half hour till 1 c.c. is given. Then 0·1 c.c. is given intravenously, the dose being doubled every 20 minutes till 25 c.c. has been given. Four hours later 50 c.c. may be given, and after 8 hours larger doses still. Various modifications of the above method have been recommended by others.

Lewis has shown that acute anaphylactic shock can be prevented in sensitised animals by giving otherwise fatal doses of diluted antigen intravenously at very slow rates. This method can be used for human beings who require intravenous injection of serum. **Woodyatt** has devised a pump operated by an electric motor and attached to the syringe. By this means as small a volume as 0·1 c.c. per minute of diluted serum can be injected into the vein. **Lewis** also investigated the route of absorption of serum on subcutaneous injection. He found that the serum was absorbed by the lymphatics. This method of absorption is too slow to account for the sudden fatal cases. He thinks that

these cases are probably due to an accidental intravenous injection of the serum.

Conclusions

1. Serum sickness with its associated skin rashes is a true anaphylactic phenomenon, and corresponds to the anaphylactic reactions in animals, allowance being made for the difference in reaction in different species.

2. Fatalities after serum injections are deaths from true anaphylactic shock resembling most closely anaphylactic shock in the dog.

3. Desensitisation or antianaphylaxis can be successfully achieved by suitable methods.

NATURAL HYPERSENSITIVENESS

In serum disease the hypersensitive state is produced artificially by injection of the serum, but there is a large group of cases where individuals are found to be extraordinarily susceptible to certain foods, animal emanations, or plants. These used to be called Idiosyncrasies. The study of anaphylaxis, however, has done much to explain many of these phenomena, and it will probably be found that, as more is discovered, they are sensitisation phenomena of varying character. It has long been known that certain persons, on eating certain foods, such as egg albumin, pork, oysters, lobsters, crab, strawberries, etc., suffer from urticarial rashes, indigestion, diarrhœa, and vomiting, etc. Hay fever and horse asthma are examples of the same phenomenon where the reaction takes place by the inhalation of the substance to which the individual is sensitive. Also it has been suggested that drug eruptions come into the same category. The fact that the symptoms are produced by minute quantities of the offending protein, that such cases give a positive cutaneous reaction to it, and that they may be desensitised by ingestion or inoculation with the protein, all point to the phenomena being anaphylactic. The fact that it is not definitely known in every case how such individuals become sensitive is not against the anaphylactic theory. It will be shown later that proteins can be absorbed unchanged through the bowel,

and that sensitisation can be produced by rubbing the juice of plants into the skin. Inhalation into the lung or absorption through the mucous membrane of the nose or throat is also possible. As already mentioned, it has been shown that guinea-pigs can be sensitised to animal and vegetable proteins by feeding the animals on them. Heredity has been shown to play a part. **Cooke** and **Van der Veer** showed that liability to asthma, hay fever, urticaria, etc., runs in families, but the actual sensitiveness of the individual is probably acquired. Members of certain families appear to be much more easily sensitised than other individuals, and it is probably this faculty of "sensitisability" that is inherited. Evidence of this will be brought forward later under plant sensitisations. In support of this also is the fact that these sensitisable individuals are often sensitive to several proteins and may become desensitised to one protein and later become sensitive to another.

THE RELATION OF ANAPHYLAXIS TO ACUTE AND CHRONIC DISEASES

As we have already seen in serum disease, the incubation period before symptoms occur and the other phenomena can be explained on the anaphylactic theory. So in infectious diseases **Pirquet** pointed out the similarity between their course and a case of serum sickness. During the incubation period antibody formation is going on, and when that is sufficiently developed an antigen-antibody reaction takes place as in serum sickness with the liberation of the toxic substance which causes the symptoms. The incubation period of most infectious diseases (8–12 days), such as smallpox, measles, chickenpox, etc., corresponds closely to the incubation period of serum sickness. **Pirquet** applied the same principle to the study of vaccinia. As the result of a primary vaccination the virus grows on the skin. About the 3rd or 4th day an elevated papule occurs surrounded by an erythematous area, and by the 7th or 8th day a vesicle is formed. These changes are due to the virus growing and multiplying in the skin. By the 8th day or so antibody is beginning to be formed and a reaction occurs with marked local pain and swelling and often general symptoms.

In this process the virus is destroyed and the vaccination heals. At this time, usually about the 10th day, a general vaccinal exanthem may occur. This rash is a bright red, slightly raised, " measly " eruption, and appears simultaneously on all parts of the skin, especially on the back, the extensor aspects of the limbs, and on the forehead, cheeks, and ears. It is usually very itchy and may go on to vesiculation. As it fades it becomes browner and develops lichenlike papules. That the body is not in the same position as it was before vaccination is shown on revaccination of the same individual. The virus introduced again into the skin a month later is at once attacked by the antigen-antibody reaction before it has had time to multiply, and in a few hours a slight reaction with only papule formation develops, which begins to involute in 24 hours. This corresponds to the immediate reaction described under serum sickness. If the revaccination takes place some years after primary vaccination, the reaction takes 3–4 days to begin, as the antibody is in slight amount or absent, but owing to previous vaccination can be more rapidly called forth, producing what corresponds to the " accelerated " reaction of serum sickness.

Pirquet suggested the term Allergy for the altered reaction capacity seen in serum sickness, revaccination, etc. He thinks it is not identical with anaphylaxis, but is included under the complex of Immunity Reactions. It is interesting to note that as far back as 1798 **Jenner** noticed during his experimental work in smallpox, that if a person had once passed through an attack of smallpox or cowpox, he may respond to the cutaneous application of the virus, if made years afterwards, by an " early local cuticular inflammation." This is the first known observation of an anaphylactic phenomenon, and describes accurately the accelerated reaction.

Of course, all the symptoms of acute diseases cannot be explained on the anaphylactic theory. The question of how many of the symptoms are due to toxines also comes in. In diseases like diphtheria the toxine produces effects quite apart from the protein of the bacteria. But taking everything into consideration, the course which acute infectious fevers run can be explained fairly satisfactorily on the assumption that they are due to bacterial anaphylaxis.

The relation of anaphylaxis to chronic diseases such as asthma, etc. has already been mentioned, but there is still the large group of chronic infections such as tubercle, syphilis, etc., which will be more fully discussed separately. All the evidence goes to show that these are examples of sensitisation to bacterial proteins.

RELATION OF ANAPHYLAXIS TO IMMUNITY

There is still difference of opinion as to the relation of anaphylaxis to immunity. **Vaughan** and his supporters go so far as to say that the mechanism in both cases is identical. They hold that in immunity the antibody is circulating in excess in the blood, and by combining with the antigen, protects the body-cells and prevents the antigen reaching the antibody in the cells, and so symptoms do not occur. The question is too complicated to discuss fully here, but the toxin-antitoxine reaction also comes in in questions of immunity. That the hypersensitive reactions play a part in the protection of the body against infection is undoubted. Local hypersensitive reactions lead to hemming in and destruction of organisms. **Danysz** and others hold that in infectious disease the individual passes through a period of hypersensitiveness before the stage of immunity is reached. That sensitisation persists after the disease dies out is an important fact. For example, it will be seen later that cases of kerion ringworm may give a positive skin reaction on the application of the ringworm fungus many years after healing. This hypersensitive state of the skin-cells leads to a local reaction on reapplication of the infecting agent, and this reaction leads to the destruction of that agent. Therefore the hypersensitive state of the individual protects him against further infection and causes for practical purposes an immunity. The same is seen in diseases such as syphilis. There is no absolute immunity to it, and so long as an individual has syphilis he cannot be reinfected. Whilst he has syphilis he is sensitised to it, and, as will be seen later, an attempt to reinoculate him leads to the production of a hypersensitive reaction which at most produces a local reaction and prevents a general spread.

Desensitisation by bacterial vaccines in infections and by protein substances in conditions such as asthma can be accomplished. This leads to at least a temporary cessation of symptoms, but does not seem to be quite the same as immunity. The effects are not lasting. All the evidence therefore goes to show that sensitisation plays a part in protecting the body against disease, but that other factors, *e.g.* toxines, are also involved.

CHAPTER III

URTICARIA INCLUDING ANGIONEUROTIC ŒDEMA

As we have already seen the most frequent rash in serum sickness is an urticaria clinically indistinguishable from an ordinary nettle rash. We have also seen that all the evidence points to serum sickness being anaphylactic. It is not a very far step to take, therefore, to suggest that urticaria also is anaphylactic in origin. This was first done by **Wolff-Eisner** in 1907, and since then many others have supported this view. **Wolff-Eisner** included all forms of urticaria both from external and internal causes; but it will be well to treat each group separately.

URTICARIAS OF EXTERNAL ORIGIN

The causes may be roughly divided into three groups:

1. Vegetable irritants such as nettles;

2. Animal irritants such as bites from pediculi, bugs, gnats, fleas, mosquitoes, etc., and stings from bees, wasps, etc.; and

3. Physical irritants such as scratching (dermographism), rubbing or stroking the skin, etc.

Vegetable Irritants

All of us have experienced the effects of handling the ordinary nettle. The wheal, which results, is typically urticarial. **Wolff-Eisner** included the nettle sting when he suggested that urticaria was a sensitisation phenomenon. With this view I cannot agree. In order to gain information on this point I experimented on myself. I stung the inner aspect of my left forearm with the leaf of the common wild nettle (*Urtica dioica*) every day for a month on the same area of skin. On the first occasion

redness appeared in 30 seconds, and in 2 minutes definite minute wheals were visible. These wheals gradually increased in size for about 40 minutes, and then slowly disappeared after about 4 hours. Immediately the nettle was applied, the usual stinging sensation was felt, which persisted at intervals till some time after the wheals had disappeared. There was never any real itching; it was more a tingling sensation. Next day, where the wheals had been, minute punctiform hæmorrhages were distinctly visible not unlike minute flea bites. On repeating the application of the nettle daily to the same area, I always experienced the same stinging sensation as at first, and the wheals always appeared in about 2 minutes or so, but they did not last nearly so long. Whereas at first they persisted for about 4 hours, at the end of a month the wheals all disappeared in about $1\frac{1}{2}$ hours. Therefore no alteration had occurred in the reaction, except that the skin seemed to show a certain degree of tolerance, but no increased sensitiveness nor immunity was produced.

I then stung both forearms simultaneously to see if there was any difference between the skin of the arm which had been repeatedly stung and that of the other arm. I found that the reaction was practically identical on both sides, but the stinging sensation was distinctly more marked and lasted longer on the arm which had not been stung repeatedly. I next crushed up the nettle leaf and rubbed it well into the skin of the arm. It produced wheals in a few minutes, and these wheals were always situated at the mouths of the hair follicles, where the juice had penetrated. No dermatitis occurred such as occurs on application of plants like the primula to sensitised individuals. This showed that my skin was not in any way sensitised to the nettle.

If a nettle sting is a sensitisation phenomenon, the first application of the nettle, like the sensitising dose in anaphylaxis, should produce no symptoms. Like practically all individuals in this country, I had been repeatedly stung by nettles before I did these experiments, therefore I could not hope to get any information on this point from adults. I therefore tested the skin of the legs of three infants at the Royal Maternity Hospital with the kind permission of the late Dr J. W. Ballantyne. These infants were normal children of 1, 10, and 13 days of age respectively. All 3 reacted within 2 minutes with the typical

nettle sting with wheal formation. I also touched the skin of one of our clinical assistants, an Australian, who, as far as he knew, had never been stung previously by a nettle, and he also reacted immediately.

From these results I conclude that the nettle sting is not a sensitisation phenomenon, but a mechanical irritation from the puncture of the skin by the fine hairs on the leaf and the injection of an irritating fluid.

Animal Irritants

Bites from insects cause reactions which vary with the insect and the individual bitten. It is well known that in some persons a mosquito bite may lead to a very great local reaction, whilst in others little or no inconvenience is experienced. **Boycott** in 1912 performed some very interesting experiments with fleas on laboratory attendants. He found that the wild rats (*Mus decumanus seu Norvegicus*) in the Pathology Department of Guy's Hospital, London, were infected with two kinds of fleas, viz. *Ceratophyllus fasciatus* (common English rat flea) and *Xenopsylla cheopis* (tropical rat flea). Both species bite man freely when given the opportunity. **Boycott** found that ordinary persons show no reaction after being bitten experimentally by either species for the first time, but he assumed that people living under ordinary good conditions in this country are not exposed to the attack of rat fleas. Two individuals were taken, A, who was known to give a prompt and extensive reaction to the bite of the human flea (*Pulex irritans*), and B, to the bite of the cat flea (*Pulex felis*). To A was fed cheopis and to B fasciatus. No effect was produced at first, but after 5 feedings in 6 weeks each gave an extensive local reaction at the site of the bite. **Boycott** therefore concludes that by repeated bites these individuals had become sensitised. Control persons who had not previously been bitten gave no reaction. To test the specificity of the reaction the fleas were reversed, fasciatus being fed to A and cheopis to B. In both cases a violent reaction was produced at the first bite. **Boycott** suggests that the absence of specificity might be due to the individual being sensitised to "ratness" rather than to "fleaness," because it is possible that the flea,

when biting, injects along with its own protein, material from its immediately preceding host. But man becomes reactive to the human flea, and that would involve the possibility of man becoming sensitised to "manness." **Boycott** thinks that it is much more likely that there is a biological similarity between cheopis and fasciatus. This would bring it into line with the findings in anaphylaxis, which are quantitatively but not qualitatively specific as regards tissues of the same group.

Eleven months later the sensitiveness of A and B was tested again. A, who had originally been sensitised to cheopis, still reacted well to it, but failed to react to fasciatus, and B, who had originally been sensitised to fasciatus, still reacted to it and also to cheopis.

Stokes in 1914 made some interesting experiments with the black fly (*Simulium venustum*), a kind of gnat of the same family as **Sambon** described as causing the spread of pellagra. These insects produce papulo-vesicular lesions, which later develop into nodules. These nodules remain for days and itch periodically. **Williams** also refers to this periodicity of itching after bites from Norwegian midges and East Anglian gnats. I can also corroborate the periodicity of itching from my own experience. Some years ago, whilst in Vienna, I was bitten repeatedly, as most people there are, by the ordinary bug (*Cimex lectularius*). The bites produced very little effect for 24 hours, but after that they swelled up into large nodules which itched intensely once or twice in the 24 hours for several days. In summer I also experience periodically itchy lesions from the bites of the ant (*Formica nigra*). **Bramwell** suggests that the periodicity of the itching may be due to the acid and alkaline wave which passes over the blood during digestion. He noticed in his own case that gnat bites were always most irritable after getting out of bed in the mornings, and the irritation did not cease till he had broken his fast. The irritation returned as soon as the stomach was empty and was relieved by the next meal. This does not agree with my own experience, which was the same as that of **Beddard,** who found that the itching recurred every 24 hours or so.

Stokes found that the bites from the Simulium flies showed, microscopically, in addition to other cells, marked collections of eosinophile leucocytes. He also states that the natives in areas

where these flies abound are practically immune to the insect, whereas strangers always react in different degrees to the bites.

Some years ago, when on holiday in Norway, I was badly bitten by mosquitoes. In me the bites caused very little reaction, but in a Scottish lady, who was also bitten, each bite swelled up to such an extent that the whole face was swollen and the eyes closed, and the arms were swollen to nearly double their natural size. On inquiry, it was found that this lady had been badly bitten by mosquitoes in Canada in the previous year. On that occasion, however, they caused very little trouble. Evidently since her visit to Canada she had become sensitised, and when bitten later in Norway, gave a very marked reaction.

Steiner found that immunity to the local manifestations of the Simulium fly gradually develops in the course of three years' residence in an infected area. When one is bitten by a blood sucking insect, it injects a fluid to prevent coagulation of the blood, and to this one probably becomes sensitised. Persons who go out to countries where flies and mosquitoes are numerous often have trouble for some time with enormous œdematous reactions from bites, but, after repeated bites, they apparently become desensitised and no longer react. This also explains the extraordinary absence of irritation among the poorer class of hospital patient from the bites of fleas and pediculi. They have been bitten so often that they are immune or at least desensitised, and as these individuals are always being rebitten, the desensitisation is kept up.

Freeman quotes **Clewes,** who had a case of a lady who lived near Lake Erie, and in whom a bite from a gnat caused such swelling that she had to go to bed for several days. **Clewes** collected gnats, bruised them in a mortar, and made a vaccine from the extract. After several inoculations the lady could lie out near the lake and " be bitten with pleasure."

Both **Stokes** and **Steiner** refer to cases where man and animals bitten by various species of Simulia, in addition to showing marked local swellings, developed a high temperature and collapsed. That insects can produce illness by introducing toxines when they bite was shown by **Moore.** He bred the *Pediculus corporis* experimentally in large numbers, and the insects were fed by being allowed to bite laboratory assistants. Persons bitten

frequently began to complain of general tiredness, severe headache, and, later, chills and rise of temperature. **Moore** himself, who was bitten by 700–800 pediculi twice daily, experienced a tired feeling in the calves of the legs, along the shin bones, and soles of the feet, so intense as to prevent sleep. He had a general feeling of irritability and pessimism. Later he developed a rash like measles and the temperature rose. The symptoms and the rash disappeared when he stopped feeding the lice, and reappeared each time when he began again. **Moore** suggests that some of the symptoms seen in trench fever may not be due to an organismal infection, but to the bites of pediculi, which introduce a toxic substance when they bite.

Stings from bees, wasps, etc., are in rather a different category. These insects inject a very irritating fluid when they sting, and everyone experiences pain and reaction on the first sting. They are analogous to the nettle sting on a large scale. The cases of death from multiple bee stings are not to be wondered at, because the amount of shock to the nervous system and the amount of poison injected must be considerable. But it is a question whether collapse or even death following one sting from a bee is not due to anaphylaxis. It is well known that those who work with bees and have been repeatedly stung become much more tolerant to stings than other people.

Conclusions

Therefore, from the fact that fleas do not cause a skin reaction after the first bite, that a reaction develops later after repeated bites, that bites from insects show an eosinophilia, and that repeated bites can lead to an immunity, I think we are safe to assume that, unlike the nettle sting, such reactions are sensitisation phenomena. Whether reactions from stinging insects are associated with sensitisation is not so clear. They may be usually due to irritant poisons, but occasionally to sensitisation.

FACTITIOUS URTICARIA OR DERMOGRAPHISM

This is the condition where wheals are produced by rubbing or scratching the skin. In some cases of urticaria wheals can be produced in this way, and it is useful as an aid to diagnosis when

no spontaneous eruption is present. In other cases it is present always in certain individuals who may never have had ordinary urticaria. Of course, if a blunt instrument is drawn across the skin, in the normal individual a faint red line appears in about a minute, and the cases of dermographism are apparently very exaggerated forms of the same reaction. **Tracey** found that mechanical irritation of the skin by stroking with a wooden instrument leads to vaso-dilatation, brief in duration, followed by vaso-constriction, which is long-lasting. He holds that it is caused by a double nerve mechanism, one of vaso-dilatation (autonomic) and the other of vaso-constriction (sympathetic). These nerve mechanisms are activated by two hormones, the hormone X of **Eppinger** and **Hess** (autonomyn), which activates the vaso-dilatation mechanism, and the hormone epinephrin, which incites the sympathetic nerve endings and activates the vaso-constriction mechanism. **Weidenfeld** also found that in cases of dermographism the skin did not react over an area anæsthetised with cocaine and that epinephrin influenced the skin in such a way that it did not react to mechanical irritation. The extraordinarily rapid effect that subcutaneous injection of adrenalin has in causing the disappearance of the rash in certain cases of urticaria is also interesting in this respect. The cases of urticaria following shocks, emotional disturbances, also may be produced in the same way, although some of them may be due to gastro-intestinal disturbances which lead to urticaria.

Gilchrist examined, microscopically, artificially produced wheals in cases of dermographism. Pieces of skin were removed 2, 5, 8, 15, 25, 40, and 60 minutes after the lesions were produced. He found an extraordinary degree of inflammatory change present. There was marked œdema of the connective tissue and fixed cells, profuse emigration of polymorphonuclear leucocytes and lymphocytes; pronounced fragmentation of the polymorphonuclear leucocytes and connective tissue cells; apparent increase in mast cells and the presence of eosinophile cells; swelling of the cells of the sweat glands with fibrin scattered through the corium. In fact, the typical picture of an acute inflammation was present, and a fragmentation of nuclei as marked as that produced by diphtheria toxine. He thinks the only possible explanation is that some toxine is circulating in the blood in these

URTICARIA.

cases, and when a wheal is produced some of the toxine is set free and produces death of cells, which is followed by acute inflammatory changes. **Hodara,** in 1913, confirmed **Gilchrist's** findings. He found the same changes in the normal skin of dermatographic patients, but with less œdema of the cutis and epidermis than when wheals were present.

Fischer produced an experimental urticaria on a gelatine plate by injecting formic acid into the gelatine with a hypodermic syringe, and then immersing the plate in water. A typical urticarial wheal resulted wherever the acid had been injected. He holds that urticarial wheals are caused by œdema due to a localised increase of acid products in the skin as a result of the anaphylactic process. These acid products lead to the tissue colloids imbibing water.

Whatever the mechanism of the wheal formation in dermographism in otherwise healthy individuals, there is no evidence to connect it with anaphylaxis.

URTICARIAS OF INTERNAL ORIGIN

Under this heading are included the ordinary urticarial rashes with small or large wheals (plate opposite), the giant urticaria with large wheals (so-called angioneurotic or **Quincke's** œdema), and urticaria papulosa in children.

As already stated, the type of the ordinary form of urticaria is the rash in serum sickness which is anaphylactic in nature. It has long been known that in certain individuals certain foods cause urticaria. Shell-fish such as crab, lobster, mussels, and oysters are very common causes, but meats, such as pork, etc., and eggs, are also frequently found to have the same effect. Meats which are tinned or which have been kept too long, *e.g.* "high" game, are also often to blame. Oatmeal, brown bread, and foods of that kind cause urticaria, especially in children, and fruits, especially oranges. It has been shown that many cases of urticaria give positive cutaneous food tests, and that is a point in favour of their being cases of sensitisation. The food tests will be referred to fully later on.

These food urticarias are usually accompanied by no other symptoms, but there are cases on record where severe symptoms

like anaphylactic shock have followed the taking of some ordinary food. **Stokes** reports the case of his own son who, on the first occasion on which he ate some raw egg-white, immediately became cyanosed, the face became greatly swollen with giant wheals and alarming collapse took place. The same thing happened when white of egg was applied to the head to keep his hair in position. The same boy could eat hard-boiled eggs with safety, but if he ate a soft-boiled egg he had a quick response with urticaria. Small quantities of foods to which such persons are sensitive will produce marked urticaria.

Intestinal parasites may also cause urticaria, but whether the patient is sensitised to the worm or the worm alters the process of digestion and allows of sensitisation to some food or bacterial substance in the bowel, is not quite clear.

It will be seen later, under Eczema, that certain persons have the faculty of absorbing proteins by the bowel and throwing them in an undigested state into the circulation. This is probably the method by which sensitisation to foods occurs.

John Thomson also reported recently a case of an infant whose mother suffered during the 4 years preceding the child's birth from attacks of urticaria, local œdema, and hay fever after eating acid fruits or bananas. During the first few months of life the baby, who was on the breast, had on several occasions a meal of cow's milk with no ill effect. When 7 months old she was given rice pudding and milk, which was followed at once by urticaria and asthma. From that time onwards she had violent symptoms whenever she was given cow's or goat's milk or raw white of egg. Half a teaspoonful of milk was sufficient to bring on an attack in a few minutes. The breathing became difficult, and there was sneezing and coughing and running at the eyes. An urticarial rash also appeared. The child was very ill, and collapsed for 2 or 3 days. All infant foods made from milk caused the same symptoms. Peptonised milk did so, but to a less degree. Raw white of egg had the same effect, but the child could take boiled and fried eggs with impunity. The above is obviously a case of hypersensitiveness, and it is interesting to note that, as others have observed, cooking the food so alters it that symptoms do not occur.

Whitfield described in 1921 some cases of what he calls auto-

sensitisation. One was a young lady who received a severe blow from a cricket-ball on the shin. A hæmatoma, without any breach of surface, was produced. Ten days later a generalised erythemato-urticarial eruption strongly resembling that seen after serum injections appeared. No other cause could be found for it, and **Whitfield** suggested that it might be connected with the absorption of broken-down tissue at the site of the bruise. The other case was in a lady who fell downstairs and damaged her left wrist, producing a severe bruise. Again, on the 10th day, a general rash appeared as in the former case.

At the meeting of the British Association of Dermatology in Edinburgh, in July 1922, **Barber** mentioned a similar case to **Whitfield's,** with an urticaria following an injury. **Barber, Wilfred Fox,** and **Skinner** also mentioned that they had seen urticaria follow in 3–10 days after amputation of the breast. In all these cases there was no sepsis at the site of the operation.

Some weeks ago I saw a lady who suffered from urticaria every time she took exercise such as dancing. Are these cases of sensitisation to products of their own tissues ? I hesitate to accept this view, as the only organ from its own body to which it is known an animal can be sensitised is the lens of the eye. In my case the exercise might produce some substance in the muscles, or there might be an increased absorption from the bowel which would account for the urticaria. It is also possible that increased circulation in the skin during exercise might excite an urticaria which would not otherwise have appeared.

Focal infections, such as tonsillitis, pyorrhœa, abscesses at the roots of teeth, infections of the bladder and bowel, etc., have all been known to produce urticaria. As an example of this, I saw recently a lady of 60 years of age who had suffered for 2 months from an extensive urticaria. She was dieted in various ways, but with no improvement. Cutaneous food tests were done to all the common foods, but all were negative. Her teeth were apparently all right, but 3 weeks or so after I first saw her she developed slight pain in a tooth. Her dentist extracted that tooth and found a small abscess at the root, and within 48 hours the urticaria disappeared and has not returned after several months now. Therefore in searching for a cause, all cases of chronic urticaria should have the teeth X-rayed for apical

abscesses. Drugs such as quinine, iodides, salicylates, formalin, etc., may also cause an urticarial rash, but these will be discussed under drug rashes.

Ravitsch reports 4 cases where removal of septic tonsils caused a rapid disappearance of urticaria. **Turnbull** also describes 2 cases of giant urticaria in which the condition was entirely relieved after removal of the tonsils and a radical sinus operation performed as the sinuses contained pus.

The bursting of hydatid cysts into the peritoneum is frequently followed by urticaria. **Chauffard, Bordin,** and **Laroche** produced anaphylaxis in animals with injections of fluid from hydatid cysts. As **Pontaro** and others have shown, a high percentage of patients with hydatid disease give a positive cutaneous reaction to cyst fluid. **Barling** and **Welsh** found that eosinophilia of the blood is present in 50 per cent. of cases of hydatid disease in a marked degree, moderate in 25 per cent., and absent in 25 per cent. **Dévé,** in 1910, reported a case of death following operation for hydatids. This he attributed to anaphylaxis. In hydatid disease, therefore, the patient seems in most cases to be sensitised to the protein of the cyst fluid, and any sudden absorption of that fluid may lead to urticaria or symptoms of shock.

Urticaria may be associated with other diseases such as malaria, rheumatism, etc., but whether it is accidental or due to sensitisation to proteins from the infecting agent is not clear.

Ward has recently noted the frequency of urticaria after specific fevers, especially pneumonia and influenza. He estimates that it occurred in 20 per cent. of his cases of pneumonia. The eruption usually occurs within a day or two after the temperature has come down to normal. Sometimes the temperature rises again slightly as the rash appears, and occasionally there are joint pains. In such cases the rash is probably a sensitisation phenomenon due to the protein of the infecting organism. After pneumonia a cutaneous reaction is present, indicating that sensitisation has taken place.

THE DUCTLESS GLANDS IN URTICARIA

Reference has already been made to these glands in Anaphylaxis. **Hoffman** found that dermographism, urticaria, asthma,

and hay fever (of which the latter two are acknowledged to be anaphylactic) are not uncommonly associated with exophthalmic goitre. **Levi** and **Rothschild** also think that urticaria is an expression of hypothyroidism, and cite cases where thyroid treatment caused rapid improvement and cure. They think that thyroid acts perhaps by its effect on the vaso-motor mechanism. **Ravitsch** agrees with this view and states that in a good many cases of chronic urticaria thyroid extract is a specific. But he also states that in cases of hyperthyroidism with urticaria, X-rays to the gland will cure the urticaria. **Barber** reports a case of chronic urticaria with enlarged thyroid whose eruption came out after the slightest exertion. Rest and removal of septic tonsils and administration of an autogenous vaccine from the tonsils brought about a great amelioration of the symptoms, with a diminution in the size of the thyroid gland. That would suggest that the change in the thyroid was secondary to the toxic absorption from the tonsils, and, like the urticaria, was a symptom of absorption and not the cause of the urticaria.

Holden also reports a case of angioneurotic œdema in a woman in whom the eruption disappeared during successive pregnancies, when the thyroid became more active, and reappeared shortly after the birth of the child. Administration of thyroid extract cured this case. Therefore it is evident that changes in the thyroid, especially a diminished function, are commonly associated with urticaria.

BLOOD CHANGES IN URTICARIA

Widal, Abrami, Brissaud, and **Joltrain** showed proof of the anaphylactic origin of certain urticarias by an examination of the blood. In a case of giant urticaria due to animal food they found all the phenomena of anaphylaxis, viz. fall in blood-pressure, diminished coagulability of the blood, and leucopenia. **Wright** and **Paramore** reported in 1905 the delay in coagulation of the blood in urticaria, which they believed to be due to a deficiency of calcium content. On the other hand, **Pepper** and **Krumbhaar** could not find any deficiency in lime salts in urticaria.

Pagniez and **Vallery-Radot** also found in chronic urticaria that the blood changes corresponded very closely to those which occurred in anaphylactic shock.

Shattock found in cases of chronic urticaria a delayed coagulation time in 4 out of 5 cases. Therefore, although the reports on the blood changes in urticaria are few, what there are support the anaphylactic theory.

HEREDITY IN URTICARIA

Cooke and **Van der Veer** showed that heredity plays an important part in asthma, eczema, and urticaria, and that certain families are much more liable than others to suffer from these diseases. **Crowder** reports a family in which numerous cases of angioneurotic œdema occurred in 5 generations. **Edgerley** and **Lush** also report angioneurotic œdema in 4 members of the same family. It is, I think, a general clinical experience that members of certain families are liable to urticaria. Heredity seems to play the same part in urticaria as it does in other sensitisation phenomenon, *i.e.* individuals of certain families can be more easily sensitised than members of other families.

DESENSITISATION IN URTICARIA

If urticaria is a sensitisation phenomenon, then desensitisation should be possible. The fact that in many cases the eruption comes out in crops, with periods of quiescence in between, favours this view. **Pagniez** and **Vallery-Radot**. in a case of giant urticaria of the face with intense ordinary urticaria of the body, by giving the patient a small quantity of the albuminous substance, which caused the eruption, 1 hour before a meal containing this substance, succeeded in preventing the urticaria coming out. Later they found that the same result could be obtained by giving 0·5 grm. of peptone 1 hour before the meal. In asthma this method of desensitisation has also been successfully employed.

THE NERVOUS SYSTEM AND URTICARIA

Even in the urticarias due to local application of irritating substances, such as the nettle sting, the nervous system may play a part in the dilatation of blood-vessels and the formation of the exudate. **Weidenfeld** in 1910 made a great many experiments on

the mechanical irritability of the skin in dermographism. He quotes the two theories as to the cause of the wheal.

1. **Ludwig's**—that by contraction of the efferent vessels together with dilatation of the afferent vessels to the skin you get a raised blood-pressure in the capillaries and the blood serum filters through; and

2. **Heidenheim's**—that the capillaries secrete the œdema-fluid and that this secretory action is produced by chemical substances.

He found that if he injected adrenalin into the skin in dermographism and produced a pale area and then stroked that area, he did not get a wheal, but a red area. Therefore a hyperæmia does not necessarily lead to an exudation even though the vessels are dilated. Injection of cocaine into the skin caused a contraction of the blood-vessels, and no hyperæmia resulted when the skin was stroked, but a wheal formed. Therefore a wheal may form in spite of the part being anæsthetic. **Weidenfeld** is inclined to support **Heidenheim's** theory and thinks that the occurrence of dermographism may be explained by irritation, from the central nervous system, of the secretory cells of the vessel walls producing the œdema. Redness or pallor occur by dilatation or contraction of the vessel walls. He did experiments by applying adrenalin in cases of dermographism, and showed that hyperæmia may be produced without exudation. This, of course, may just be a question of the chemical constitution of the toxine. In urticaria due to bee or wasp stings it is probably the chemical substance injected which calls forth the exudate, presumably by chemotaxis; so also in nettle stings. If in dermographism the cells of the vessel wall secrete a chemical substance (ferment ?), that substance would call forth a serous exudate and hence the wheal. But why should the vessels secrete this ferment in some people and not in others ? **Kreibich** holds an almost similar view that wheals are due to irritation of cells of the sympathetic nervous system through sensory irritants. He thinks that the sympathetic ganglia are not diseased, but are hyperexcitable. **Hazen** considers that it is impossible to study the phenomena of sensitisation without considering the vegetative nervous system. He thinks that all the cases of urticaria following frights, emotional disturbances, and the case of **Hebra's,**

which followed the passage of a uterine sound, were due to vagus irritation.

Samberger also regards urticaria as an endocrine disease in which the vagus dominates the sympathetic, and therefore hyperæmia and exudation develop. He thinks that in the wheal there is a sympathetic ischæmia, and this want of blood with its accompanying oxygen is registered in the form of a final hyperæmia and wheal formation. He quotes the beneficial effect of injecting atropin in urticaria in favour of his opinion.

Török holds the opposite view, and thinks the nervous system has nothing to do with the formation of wheals. He found that a large variety of substances, such as ptomaines, sera, bacterial toxines, and drugs, produced urticarial lesions when introduced into the corium. He thinks they act by injuring the vessels and by repeated application bring about a hypersusceptibility of the vascular system. He cites **Gilchrist's** finding of inflammatory changes in the wheal in support of his view that the wheal is due to the presence of a circulating toxine.

Unna's theory that the wheal is due to a spasmodic contraction of the venules has no longer any great support. **Neisser** thinks it is a vaso-motor neurosis with dilatation of the vessels. **Neisser** on the dog's tongue, and **Bruck** on the frog's tongue, produced an œdema by prolonged irritation of the glosso-pharyngeal nerve with a faradic current. **Bruck** examined the tongues microscopically and found only œdema without inflammatory changes. **Kreibich** also attributes the wheal to nerve influence. On the other hand, there are many, including **Gilchrist, Philippson,** and **Török,** who hold that the wheal is a local inflammatory lesion due to a toxine without the influence of the nervous system. As all the reactions of inflammation are intimately bound up with the nerve mechanism of the vessels probably both the nervous system and a local irritation play a part.

WHAT EVIDENCE IS THERE TO SUPPORT THE ANAPHYLACTIC THEORY OF URTICARIA DUE TO INTERNAL CAUSES ?

Before discussing this question some experiments performed by **Bruck** must be referred to. **Bruck** tried to produce anaphy-

laxis in animals with substances which are commonly the cause of urticaria in the human subject. He showed that both active and passive anaphylaxis could be produced with pig serum and the fresh muscle of the river crayfish. He also quotes the case of a man who suffered from urticaria every time he ate swine flesh. He withdrew blood from this man, separated the serum, and injected it into 3 guinea-pigs in doses of 10 c.c. As controls, other 3 guinea-pigs were injected with 10 c.c. of normal human serum. Twenty-four hours later 2 of the first set of animals were injected intraperitoneally with inactivated pig serum and showed typical anaphylactic shock. The third animal of the first set was injected with sheep serum with no result. The second set of animals was injected with normal human serum similarly to the first set, but no shock resulted. Therefore **Bruck** concludes that, because the serum of a patient with urticaria due to swine flesh could induce passive anaphylaxis in normal animals, urticaria is a true anaphylactic phenomenon. **Bruck's** experiment seems to be an isolated one and has not been confirmed.

Another point in favour of urticaria being anaphylactic is the fact that in sensitive persons very small quantities of the offending food may cause the urticaria. So also a very small focus of absorption, such as a minute abscess at the root of a tooth, may cause a widespread urticaria. In both these cases the amount of actual food or poison absorbed is too small to account for the symptoms except on the sensitisation theory. The fact that urticaria from a given food may occur on the first occasion on which a child gets that food, is not against a previous sensitisation. I have seen a case of urticaria in an infant on the breast. The urticaria occurred every time that the mother took eggs, so that a child may become sensitised through the mother's milk. When the above child later was first given egg, had it developed urticaria it would have been quoted as a case showing the rash on the first occasion on which eggs were eaten. The periodic occurrence of crops of eruption is also in favour of sensitisation, the intervals representing periods of temporary desensitisation. The fact that the cutaneous food reactions may be positive one week and negative the next, and then positive again later, supports this contention. Urticaria is

common in members of families which suffer from such sensitisation phenomena as asthma and hay fever. The blood changes in urticaria also closely approximate to those found in anaphylaxis. Desensitisation with peptone, etc., has also been successfully accomplished.

Therefore the evidence on the whole is in favour of urticaria and angioneurotic œdema of internal origin being a true anaphylaxis.

CHAPTER IV

DRUG ERUPTIONS (Exanthemata)

In this section are included only the rashes which occur after the administration of drugs, whether given by the mouth, injected subcutaneously, intramuscularly, or intravenously, or from absorption through the skin, as when a general rash appears after the local application of belladonna plaster. The rashes produced locally by the external application of drugs to the skin will be considered separately under Dermatitis Venenata.

It is not necessary here to enumerate the drugs which commonly cause rashes, nor to describe the kind of rash which each drug usually produces. The rashes may be urticarial, erythematous, papular, vesicular, bullous, squamous, pustular, purpuric, nodular, or ulcerative. They are usually uniform in type in each case, but may be multiform. They may appear soon after the drug is given or only after prolonged administration. Defective elimination in renal and cardiac disease undoubtedly predisposes, but is not the true cause, as rashes may occur in perfectly healthy individuals.

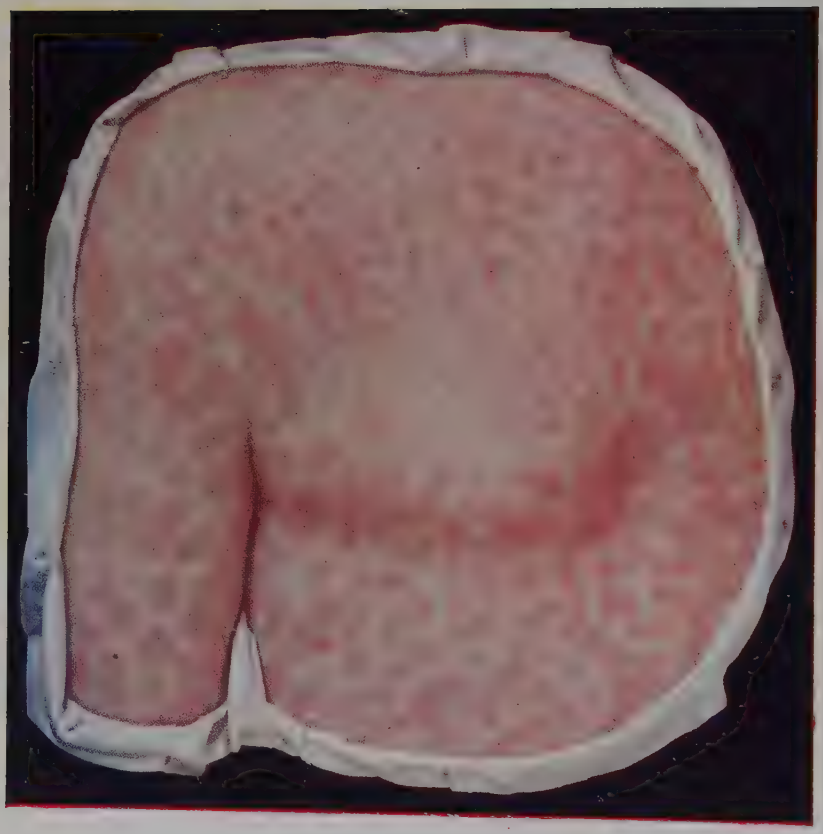
The fact that in certain individuals even small doses of a drug given once, or only for a short period, in which a cumulative effect could not occur, may cause a rash, suggests that the rash may be a sensitisation phenomenon. A certain amount of experimental work has been done to try to elucidate this question.

Bruck describes the case of a doctor who took antipyrin for headaches. Whenever he took the drug he developed swelling of the lips and tongue, with ulceration and an itchy dermatitis on genitals on one occasion. Sixteen years after this doctor had last taken antipyrin, **Bruck** used his serum to sensitise guinea-pigs passively. He first determined the dose of antipyrin which a guinea-pig could tolerate. He succeeded in producing what

he considered passive anaphylaxis in the guinea-pig by first injecting the patient's serum, and 24 hours later a dose of antipyrin. He therefore concludes that antipyrin idiosyncrasy is dependent on a true anaphylaxis. He did not succeed in producing passive anaphylaxis in guinea-pigs with the serum of patients with an idiosyncrasy to mercury. He also quotes **Liebkind** as getting a similar negative result. These cases, however, must be looked upon with suspicion. Was **Bruck's** case really a case of an antipyrin exanthem ? The fact that the swelling and ulceration took place on the tongue and lips where the drug was in contact, points to its being a case where the mucous membrane was sensitive and the dermatitis on genitals might have been due to some of the antipyrin getting transferred there by handling. It looks more like a case of dermatitis venenata due to antipyrin than a real exanthem. Therefore his conclusions apply to that condition and not to the true drug exanthem.

Klausner found that animals injected with serum from patients who showed iodide rashes after taking potass. iodide, and then later injected with 0·5 grm. KI, always showed the same symptoms, viz. collapse, dyspnœa, and death within an hour ; whereas the control animals injected first with normal serum showed no symptoms. Two of **Klausner's** patients developed a rash on the first occasion on which they took KI. So far as could be ascertained, neither had had any KI before on any occasion. He suggests a congenital sensitiveness. It is possible that they might have got KI through their mothers whilst on the breast, or as children been given KI in cough mixtures, etc. Iodine is an unfortunate drug to experiment with, as it is contained in the thyroid secretion, and so may be absorbed into the system from that gland.

Cole, in criticising **Bruck's** and **Klausner's** results, thinks that their experiments were not sufficiently controlled and that the doses of KI used were too large and too strongly hypertonic, and, therefore, the results might have been toxic reactions. **Cole** himself repeated **Bruck's** and **Klausner's** experiments. He obtained serum from 3 cases. One was a man who showed an erythematous and pustular iodide rash. Another was a man with a petechial iodide rash, and the third was a non-



COPAIBA RASH.

susceptible man who had been taking KI in 2-grm. doses, t.i.d., for 6 months. The serum of these 3 cases was injected into guinea-pigs, and subsequently a non-lethal weakly hypertonic dose of KI given. Many animals were used, and controls using human serum were made. Five of the 26 guinea-pigs died in a sudden acute manner that was quite inexplicable. Some of them died with convulsions, others fell over, panted, became paralysed, and died. Others just became apathetic, listless, then paralysed, and died. On post-mortem examination nothing was found except a general congestion of the internal organs. There were no hæmorrhages into the lungs or stomach, no œdema or distension of the lungs, and no fatty change in the heart muscle. Therefore **Cole** does not think that they died of true anaphylaxis. He entirely agrees with **Bruck** and **Klausner** that tuberculin exanthemata are due to anaphylaxis, and that it can be transferred passively ; but he does not think that the drug rash is the same as the tuberculin rash. Tuberculin is a protein substance, whereas KI has no protein. **Bruck** suggested that the iodine combines with albumin and forms an iodo-albumin to which the patient is sensitised. **Ford,** on the other hand, has succeeded in immunising animals to a hæmolytic glucoside derived from a poisonous mushroom. This glucoside contains no protein. **Cole** thinks that **Bruck's, Klausner's,** and his own results with iodides show that in some cases animals previously injected with serum from sensitive patients, and then with KI, may die with symptoms resembling anaphylactic shock, but does not think we are justified in calling it a true anaphylaxis. As already mentioned, substances such as kaolin, starch, agar, pectin, and histamine can, when treated with serum, produce symptoms like anaphylaxis. Histamine, which is an amin derived from histidin obtained from the sap of a cotyledon plant, was used by **Kritchewsky, Smith,** and others to produce symptoms like anaphylactic shock. But **Smith** showed that the blood changes and temperature reaction in histamine shock are not those of anaphylaxis, and most workers are agreed that the shock produced by non-protein substances like histamine is not true anaphylactic shock. In a man with a morbilliform copaiba rash **Cole** had no success in the passive transference of the susceptibility to guinea-pigs.

Volk also did a number of experiments in order to see whether iodine-containing substances combined with albumin and so produced an iodine protein, which might cause anaphylaxis. He injected guinea-pigs subcutaneously with iodoform and later injected iodised horse serum without producing any symptoms of anaphylaxis. He also made a series of experiments to produce active anaphylaxis in animals by repeated injections of antipyrin, quinine, and arsenic, but the results were negative. This corresponds with the results of **Klausner,** who found that guinea-pigs already anaphylactic to serum, show more severe symptoms on injection with antipyrin than do normal guinea-pigs. **Volk** also attempted to produce passive anaphylaxis. The blood of a patient recovering from an arsenical rash was injected into a guinea-pig, and 24 hours later a dose of sod. arsenate was injected with no result. So also the blood of a patient with a quinine rash was injected into 4 guinea-pigs, and each was given later a dose of quinine. The result was nil. **Volk** thinks that true anaphylaxis can only be produced by albumin bodies. Symptoms of paralysis or a kind of shock may be produced, but he does not consider it a true anaphylaxis. **Volk** quotes a case of syphilis which developed a dermatitis of the skin from the application of mercurial ointment, and also a general rash and symptoms of intoxication when the tonsils were painted with a solution of mercury, and severe symptoms on taking KI. Yet this patient could tolerate injections of grey oil and corrosive sublimate quite well. He also had another similar case who developed a rash when he took mercury by the mouth, but not when it was injected intravenously. Therefore he concludes that it is a cutaneous hypersensitiveness (not anaphylaxis). This will be referred to later under Dermatitis Venenata.

Dörr tried to produce passive anaphylaxis to strychnine in animals, but without success. He does not consider the symptoms sometimes produced by repeated injection of drugs as true anaphylaxis.

Kyrle did a number of experiments with animals, injecting them first with the serum of patients who showed rashes on taking mercury, codein, or bromide, and then with the drug. Like other workers, his results show that such animals have more marked symptoms than normal animals and an immediate

reaction, followed sometimes by death. The symptoms were not exactly like anaphylactic shock. The experiments with bromides and iodides, which are not such poisonous drugs as mercury and codein, were all negative. It is significant that reactions and death only occurred with the use of large doses of the drugs, and not with small doses, as should occur if it were a true anaphylaxis.

Zieler also holds that **Bruck, Klausner,** and the other workers have not proved their contention that the serum of patients with an idiosyncrasy to drugs can produce a passive anaphylaxis in animals. He injected animals with the serum of a case which showed a rash on administration of fibrolysin, of a case of iodide rash, and of a case of antipyrin rash, and then gave them a dose of the drug. In all cases he got a reaction which he attributed to poisoning. He admits that the previous injection of the serum intensified the symptoms, but states that the clinical picture of poisoning from a drug such as antipyrin is somewhat like that of anaphylaxis.

Friedberger and **Tetsuta** did experiments on the influence of iodides on guinea-pigs by repeated administration. They injected iodalbumin (prepared through iodisation of guinea-pig serum) into guinea-pigs. On reinjection with this iodalbumin, no definite hypersensitiveness was shown. But on reinjecting the animals with sod. iodide, signs of hypersensitiveness occurred ; so also on reinjection with Lugol's solution of iodine and with iodoform. By injecting guinea-pigs first with Lugol's solution, hypersensitiveness occurred on reinjection with iodalbumin, but not on reinjection of sod. iodide or Lugol's solution. They also found that animals previously treated with iodalbumin and reinjected with homologous iodalbumin were anti-anaphylactic to a third injection of iodalbumin. These experiments seem to support **Bruck's** view that in iodide and iodoform sensitiveness the reactions are due to the iodine combining with albumin to form a compound to which sensitiveness may occur.

Cooke thinks that hypersensitiveness to drugs is allergic in nature and not to be confused with exaggerated normal reactions, which he thinks should be considered as " idiosyncrasies." As proof of the allergic nature of drug reactions, he quotes the influence of heredity. In 15 cases quoted, a positive antecedent

history of hypersensitiveness existed in 12, and in the other 3 cases there was evidence of allergy, such as asthma, hay fever, or urticaria, in the individual himself. The symptoms in drug allergy are separate from the normal or toxic action of the drug, and are the same as occur with foods, pollens, and animal emanations, viz. corzya, cough, bronchial spasm with urticaria or angioneurotic œdema in some cases, and frequently intestinal disturbances with vomiting and diarrhœa. In practically all there is an eosinophilia of from 10 to 15 per cent.

Wile, Wright, and **Smith** in 1922 investigated bromide and iodide eruptions. They found that the pustules are not sterile, but consider that the bacteria present are probably secondary contaminations. Iodide and bromide could not be found in the purulent material from the lesions, although they could be demonstrated in the sweat and in the blood serum after ingestion of the drug. The percutaneous introduction of foreign protein in the presence of a circulating blood containing bromide resulted in 1 case in lesions simulating those produced spontaneously by bromides. They think this reaction parallel to the positive luetin test (to be referred to later) obtained when iodides are being taken. Precipitins in the blood serum were not demonstrable in vitro by the addition in minute quantities of bromide and iodide salts to the blood sera. These authors think that the local phenomena of iododermia and bromodermia do not find their explanation on simple bacterial or chemical grounds, and the ultimate explanation probably lies in a complex bio-chemical reaction. They conclude that the classification of such cutaneous phenomena as sensitisation or allergy is as yet unjustifiable in the light of our present knowledge.

During the last few years a good deal of attention has been paid to the rashes which follow the administration of salvarsan, arsphenamin, novarseno-billon, and similar preparations. On repeated injection of these drugs the so-called " nitritoid crisis " may occur. Death may even occur as in **M'Donell's** case, who received 2 intravenous injections of 0·6 salvarsan at intervals of 8 days. The first injection had no ill effect, but 48 hours after the second injection there was a marked rise of temperature, cerebral symptoms, with convulsions, difficulty in breathing, and death on the 4th day from stoppage of the respiration.

Several similar cases have been recorded by **Wechselmann** and others, and symptoms seem to occur more frequently with one batch of material than with another. **Marchalko** and **Veszprenie,** who examined the brain in such cases, found multiple hæmorrhages which they attributed to the toxic effect of the drug. But, apart from these general symptoms, rashes have been frequently observed. These may be urticarial, erythematous, and scarlatiniform. But the most striking is a general erythema, with desquamation very closely approximating to the rash of general exfoliative dermatitis. This eruption, after persisting for some weeks, fades, and the patient recovers completely. As will be seen later, general exfoliative dermatitis is probably a sensitisation phenomenon, and these rashes after salvarsan, etc., run a very similar though shorter course to that disease.

The cases of acute nitritoid crises after injection of imperfectly alkalinised solutions of arsphenamin clinically resemble anaphylactic shock. **Swift** has shown that guinea-pigs could be sensitised by the injection of a mixture of guinea-pig serum and salvarsan, and on reinjection, after a suitable interval, with the same mixture, show symptoms identical with anaphylactic shock. He thinks that in man a similar reaction occurs by the salvarsan combining with his blood serum to form a mixture which acts as a foreign serum. **Swift** found that a guinea-pig never shows an anaphylactic reaction with untreated homologous serum. Injection of salvarsan alone does not render a guinea-pig hypersensitive to a subsequent injection. Symptoms are only produced when the mixture of salvarsan and serum is used. **Swift** states also that the hypersensitive condition induced in patients by repeated salvarsan injections passes off after a certain time and treatment may then be resumed, but in some cases later injection may cause worse symptoms corresponding to the immediate or accelerated reactions seen in serum disease. If a small preliminary dose be given before the full dose a state of anti-anaphylaxis or desensitisation can be produced. **Emery** and **Morin** and others have adopted the method of giving small and progressively increasing doses at frequent intervals to prevent a reaction. The fact that a nitritoid crisis may occur after the first injection, seemingly ruled out anaphylaxis, but, as **Stokes** points out, the newer physical conceptions of the mechanism of anaphylactic shock

being due to a dispersion of the colloids of the blood serum may give the explanation. **Danysz** has shown that the arsphenamin solution is essentially colloid, and that on its injection the arsphenamin base is precipitated out by the constituents of the blood plasma. If the solution is imperfectly alkalinised, or if the serum of the patient is abnormal, rapid precipitation, followed by an acute reaction, ensues. **Stokes** therefore considers the reaction to arsphenamin as a form of anaphylactic shock. The nitritoid crisis, as shown by **Milian** and others, can be inhibited by previous injection of atropin as in anaphylactic shock.

The production of anti-anaphylaxis, as mentioned, further supports the anaphylactic theory. **Stokes** and **Cathcart** found no clinical evidence to support the contention that rashes and symptoms after administration of arsphenamin were due to retention of the arsenic by injury to the kidney from the mercury which is often given. In many cases with rashes they found evidence that chronic focal or intercurrent infections may play a part in producing the eruption. They have seen serious and even fatal results with rapid extension and generalisation of a previously mild dermatitis following the stirring up of a focus of infection, and removal of a septic focus has resulted in rapid disappearance of a severe dermatitis. They suggest that the post-arsphenamin dermatitis is based on an allergic instability produced either by colloidal changes secondary to arsphenamin injection or chronic or sudden absorption of bacterial sensitising protein from a focal or acute infection. In 33 cases of cutaneous eruptions after arsphenamin, 9 had severe eruptions of the general exfoliative type. Of these 9, 80 per cent. had serious degrees of septic focal infection in gums or tonsils. In 12 cases of milder cutaneous rashes, either erythematous or urticarial, only 17 per cent. had any degree of infection. Of the 33 cases, in only 6 could no focus of infection be demonstrated. In practice they find it better not to remove a focus of infection during the attack of dermatitis in case it causes an exacerbation of the rash. They are best removed before treatment with the drug or after the dermatitis has subsided. The cases of the sudden onset of an exfoliative rash following the application of external irritants such as tinct. iodi. or inunction of mercury, they explain as being due to the same cause as the dermatitis which **Auer** produced

by applying xylol to the ears of sensitised rabbits. The external irritant causes a vaso-dilatation and brings a larger amount of antigen to the sensitised cells, and so the dermatitis results. **Stokes** and **Cathcart** regard these reactions as not truly anaphylactic, but prefer to call them cases of hypersensitiveness or allergic instability. **Hanzlik** and **Karsner** suggest that they should be considered as " anaphylactoid." **Pomaret, Danysz,** and others have suggested that the nitritoid crises following the injection of the arseno-benzol compounds are due to a precipitation in the blood. If a slightly acid solution of these drugs is added to an albuminous solution in vitro, a precipitate consisting of a combination of the protein with the drug results. But **Schamberg, Kolmer,** and **Reiziss** showed by experiments that alkaline solutions of arsphenamin do not cause precipitation in the presence of organic or inorganic constituents of the blood. The same workers also tested the hæmolytic activity of arsphenamin, and found that it is hæmolytic in practically all the concentrations in which it is employed, whereas neo-arsphenamin is not hæmolytic except in very dilute and very concentrated solutions. The injection of cloudy or turbid solutions of neo-arsphenamin will almost invariably give rise to severe nitritoid symptoms. But nitritoid crises may follow the injection of clear solutions. Whilst admitting that acid solutions of arsphenamin may cause intravascular precipitation, the above authors do not think that nitritoid crises are due to a precipitation, but to some undetected impurity in the drug. In no other way can the variation in the incidence of reactions with different lots of brands of the drug be explained.

In cases of marked intolerance to drugs of the arseno-benzol group **Tzauk** tried to produce a passive anaphylaxis in the guinea-pig by the preliminary injection of the patient's serum followed the same or next day by arseno-benzol. At first all attempts failed, but by altering the technique and giving the injection direct into the heart he succeeded in 4 cases in producing a definite typical anaphylactic shock in the animal. Controls carried out by the injection of serum alone and the arsenical salt alone failed to produce symptoms of shock. Also controls performed with the serum of 3 normal individuals gave rise to no anaphylactic reaction in the guinea-pig. There-

fore he claims to have produced passive anaphylaxis in the guinea-pig.

BLOOD CHANGES FOLLOWING THE INJECTION OF ARSENICAL COMPOUNDS

Mackee found that, although there was a fall in the number of red blood corpuscles after injections of salvarsan in cases of reaction after injection, there was no hæmolysis. He found no appreciable increase in the leucocytes, but differential counts showed an increase of polymorphonuclear leucocytes and diminution of lymphocytes. **Moore** and **Foley** in severe reactions to salvarsan and the diarseno-benzol brands of arsphenamin found a leucopenia. Differential counts demonstrated an increase in the large lymphocytes and an increase in the eosinophile leucocytes.

CUTANEOUS REACTIONS IN DRUG RASHES

Zieler asks the question whether a cutaneous reaction, if present, cannot be used to test the sensitiveness of a patient to salvarsan. Twenty-one cases were tested by the intracutaneous injection of salvarsan. Injection of 0·001 gave a positive reaction in almost all the cases, and injection of 0·0001 a positive result in only 4 of the cases. Some of these cases had been previously treated with salvarsan and others had not, and in those patients who showed a marked cutaneous reaction subsequent injection of the drug caused no symptoms. Therefore he concludes that any skin reaction which can be obtained with salvarsan is due to chemical irritation and is not a sensitisation phenomenon. Several other observers have reported local reactions at the seat of injection of arseno-benzol preparations.

Azua describes a case which had had 2 injections of salvarsan, the second 12 days previously, and in whom an injection of arsenic and strychnine caused the formation of an urticarial wheal at the seat of injection. He interpreted that as a local anaphylactic phenomenon.

Cooke describes the production of violent bronchial asthma in 9 cases by the administration of 10 grs. of acetyl-salicylic

acid. In 3 of these cases urticaria was also present. Positive cutaneous reactions to acetyl-salicylic acid were only obtained in those cases where there was a clinical history of urticaria. In 1 case a general reaction followed the intradermal test with 0·1 gr. of the same drug. **Cooke** does not think these reactions specific for the drug, but dependent on a fraction of the chemical molecule, as symptoms might occur with acetyl-salicylic acid and not with salicylic acid, methyl-salicylate, etc. **Boerner** experimented with himself. He was susceptible to quinine, and suffered from a rash with intense itching of the skin when he took the drug. He scarified a small area of his skin and rubbed in powdered quin. sulph. In 5 minutes the abrasion began to itch, and in 10–15 minutes the area became œdematous in the centre with an area of erythema around it 1 inch in diameter. As 6 other individuals who were not susceptible to quinine gave no reaction to the same test, **Boerner** concluded that the reaction was specific and not due to the irritation of the quinine. Solutions of quin. bisulph. in strengths of 1 in 10, 1 in 200, 1 in 500, and 1 in 1000 were also used, and **Boerner** found that he got the best reaction with a solution of 1 in 10. With that strength of solution the reaction was more marked than with powdered quinine. Guinea-pigs inoculated with **Boerner's** serum and then 48 hours later with quinine failed to show any sign of anaphylaxis.

Mook quotes the case of a medical student who developed an erythematous rash after taking quinine. This student gave a positive cutaneous and intracutaneous reaction to a solution ($\frac{1}{5}$ gr. in 1 c.c.) of quin. hydrochlor. in normal saline solution.

Edlavitch also confirms these observations in a person sensitive to quinine. With a 10 per cent. aqueous solution of quin. sulph. he obtained a marked cutaneous reaction with wheal formation and erythema. The reaction reached its maximum in about half an hour, and disappeared within a few hours. The control area did not react. The test was repeated a fortnight later with the same result.

O'Malley and **Richey,** in 2 cases with erythematous rashes following the administration of quinine, found the skin test with a 10 per cent. solution of quin. sulph. a good index of hypersensitiveness. The intensity of the cutaneous reaction was found

to be in inverse ratio to the degree of sensitiveness of the patient. These cases reacted to the various salts of quinine only, but failed to react to cinchonin, cinchonidin, salicylic acid, caffeine citrate, potass. iodide, atropin sulphate, and epinephrin. On desensitising these cases by giving a preliminary small dose of quinine before each therapeutic dose, the cutaneous reaction gradually diminished and disappeared on the 10th day.

The experiments of **Smith** have some bearing on the sensitiveness to quinine. He found that guinea-pigs and rabbits sensitised to ox or horse serum, if treated with moderate doses of quinine preceding the reinjection of the specific antigen, had their susceptibility increased from 3 to 10 times as compared with control sensitised animals.

Wile, Wright, and **Smith** found that percutaneous tests with solutions of iodides and bromides were uniformly negative in cases with rashes from these drugs. In one case of an extensive bromide rash in an epileptic in which I did a Pirquet test with a 10 per cent. solution of pot. brom. the result was negative. Both the control and the area treated with the bromide solution showed a wide erythema, but no wheal formation resulted.

Therefore, except for the cases of quinine rashes, a positive cutaneous reaction does not seem to occur in cases of drug hypersensitiveness, and the skin test is not reliable as a guide as to which drug is producing a rash; nor is the test of any value to determine whether a drug may be given to a patient with safety.

DESENSITISATION TO DRUGS

In a case which developed an urticarial rash on the administration of quinine, **Heran** and **St Girons** gave 0·5 mgrm. quin. sulph. 1½ hours before the ordinary dose, and found that by that means no symptoms occurred. **Laroche, Richey,** and **St Girons** also found that hypersensitiveness to quinine could be overcome by giving 1 mgrm. quinine and 0·5 grm. sod. bicarb. 1 hour before the therapeutic dose. **O'Malley** and **Richey** in their 2 cases of quinine rash found the above method quite efficacious in one case, but in the other it only increased the tolerance but did not completely prevent symptoms.

Widal and **Vallery-Radot** report a case of sensitiveness to

acetyl-salicylic acid. The drug was given first in a dose of 0·005 grm. and 1 hour later in a dose of 0·25 or 0·5 grm. This was repeated 13 times in 6 weeks, the preliminary dose being gradually increased from 0·005 to 0·03 grm. This sufficed to prevent all symptoms. They also record a case of a woman, aged 24, who took antipyrin for headaches every month. During 9 years no bad effect was noticed, and then suddenly every time she took the drug she suffered from intense itching of the chin and lips, which became red and swollen. **Widal** and **Vallery-Radot** tried to find how small a dose could be given without producing symptoms, and found the dose to lie between 0·0001 and 0·0002 grm. The administration of such small doses for 2 months completely desensitised the patient, so that antipyrin could be taken in ordinary doses without discomfort. Desensitisation to drugs of the arseno-benzol group has already been referred to.

Therefore desensitisation either by preliminary small doses before each therapeutic dose or by repeated prolonged administration of minute doses can be successfully accomplished.

Adrenalin injected in a dose of 1 c.c. (of 1 in 1000 solution) 15 minutes before each injection of salvarsan was found by **Nageli** to prevent the appearance of an erythematous rash and other toxic manifestations which otherwise had always previously appeared. As adrenalin is known to control some cases of recurrent urticaria, especially the cases associated with asthma, the above case is another point in favour of the anaphylactic origin of salvarsan rashes.

GENERAL CONCLUSIONS ON DRUG RASHES

1. The type of rash seen after the administration of drugs is usually of the urticarial and erythematous type, such as is seen in serum sickness. Papular, pustular, or nodular rashes may be due to the same reaction localised to the follicles, sweat or sebaceous glands, through which the drug might be excreted. Similar rashes occur in the tuberculides and trichophytides which are definite sensitisations.

2. The fact that a patient may tolerate a drug for a long time and suddenly develop a rash, which occurs later on each

administration, even although the drug has not been taken recently, excludes a cumulative effect and supports the sensitisation theory.

3. The latent period after taking the drug before the rash appears also corresponds to that seen in serum rashes.

4. The rashes are specific up to a point. All drugs of the same group give reactions, such as copaiba, cubebs, and turpentine, which are all allied balsamic substances.

5. Experiments on animals to produce active anaphylaxis to drugs have been negative.

6. Experiments on animals to produce passive anaphylaxis to drugs were on the whole negative. A reaction was found which is probably not true anaphylaxis.

7. The "nitritoid crisis" following the administration of arseno-benzol compounds, is probably not a true anaphylaxis, but may be a closely allied phenomenon.

8. Focal infections may have some bearing on the production of rashes after arseno-benzol.

9. Blood examinations are too few from which to draw conclusions.

10. The cutaneous test, except in the case of quinine rashes, has given disappointing results.

11. Desensitisation to drugs has been successfully accomplished.

12. Drug rashes have not been proved definitely to be phenomena of true anaphylaxis, but the reaction caused by drugs is probably an allied phenomenon, and in the present state of our knowledge probably best described as "anaphylactoid."

ERYTHEMA IRIS.

CHAPTER V

THE ERYTHEMATA, INCLUDING E. MULTIFORME, E. SCARLATINIFORME, E. NODOSUM, AND PURPURA

General Erythemata resemble in many respects the exanthemata and are admittedly toxic in origin. They are closely allied to and often accompanied by urticarial lesions. The large group due to foods, drugs, bacterial toxines, etc., is the same type of rash as is seen in serum sickness and probably is due to the same cause, viz. a sensitisation to some protein. As these have been discussed under serum sickness, urticaria, and drug rashes, they require no further comment.

Erythema exudativum multiforme, however, is a distinct clinical entity, and therefore require sfurther discussion. I think the cases following the taking of drugs, food, toxines, bacterial infection, etc., should be separated from the true E. multiforme. The former really fall better into the group of general erythemata of multiforme type. To this group belong cases like that of **Corlett's.** His case was that of a boy who was shot behind the left ear, and 8 days later developed a general eruption with erythematous lesions with blebs arranged in a circinate manner. The blebs contained a pure culture of the streptococcus, which had evidently gained entrance at the gun-shot wound.

The typical Erythema Multiforme cases are those in which the eruption occurs chiefly on the hands, face, and feet with erythematous, circinate, papular, vesicular, bullous or irislike lesions. The eruption recurs at intervals and often for no apparent reason. In some cases, however, a typical E. multiforme may follow a definite lesion. **Norman Walker** in 1901 described 4 cases following vaccination against smallpox. Similar cases have been described by **Fox** and others. **Osler** described cases of erythema multiforme associated with visceral

lesions such as disorders of the gastro-intestinal tract, damage to the kidney, cerebral symptoms, etc. He pointed out the similarity between these cases and serum sickness. **Christian** also described a group of similar cases with erythematous, urticarial, or purpuric lesions associated with visceral lesions. From analogy with serum sickness these cases are obviously anaphylactic. **Anthony** quotes a case of E. multiforme associated with infected teeth and enlarged glands; also cases with pus infections of the urinary tract with enlarged prostate. Pharyngitis and other throat conditions may also be followed by E. multiforme. He also quotes a case of **Sabrazes'** in a labourer who over-exerted himself for a long time in order to stimulate his companions to complete some work. This man developed E. multiforme possibly owing to absorption of muscular products. This type of case, however, is not likely to occur frequently to-day! **Anthony** explains the frequency of E. multiforme in spring and autumn as due to alterations in food and clothing at these periods, and therefore alteration in elimination. Foods have been frequently reported as causing E. multiforme. **Engman** described the case of a girl who had an attack of E. multiforme every time she ate pork chops; **Galloway,** a case due to eating blackberries and nuts; and **Fordyce,** a case of E. iris after eating lobster.

Rheumatic symptoms are frequently associated with E. multiforme, although not so frequently as with E. nodosum. But E. multiforme is not associated with true rheumatic fever, and any rheumatic symptoms are possibly due to absorption from the throat or other septic focus.

Epidemics of E. multiforme have been described. These may be due to some special article of tainted food, and **Herxheimer** describes an epidemic of 14 cases among soldiers in barracks. Disinfection of the rooms stopped the epidemic.

Cuiffini and **Lyonnet** and **Martin** tried to show a connection between E. multiforme and tuberculosis, but the association of these two conditions was probably only a coincidence.

Conclusions

From the resemblance of the lesions in E. multiforme to those in urticaria and serum sickness, the former disease is probably

ERYTHEMA NODOSUM.

anaphylactic like the latter. In some cases the condition is due to sensitisation to a definite substance, such as a food or drug, but in others it is often difficult or impossible to trace the actual source of absorption. The teeth, throat, nose, accessory sinuses, gastro-intestinal or urinary tracts may be the seat of some infective process, and the patient is sensitised to the protein of the infecting organism. The relapses, alternative with periods of freedom from eruption, also correspond to what occurs in urticaria. There is, however, no evidence to show why in one case a sensitisation leads to a true urticaria and in another to erythema multiforme. Further work is necessary to elucidate this point.

ERYTHEMA SCARLATINIFORME

Apart from generalised scarlatiniforme rashes due to drugs such as quinine, enemata, ptomaine poisoning, etc., a recurrent scarlatiniforme erythema very closely resembling scarlet fever may occur. This rash is followed by desquamation. Nothing is known as to its cause, but as it is not contagious it is probably not due to an infection like the fevers. From its resemblance to toxic rashes it is possibly a sensitisation phenomenon. In favour of this is the recurrence of the rash after intervals of freedom and the gradual diminution in the severity of the attacks till they cease altogether. Presumably each attack temporarily desensitises the patient, and after several attacks a complete immunity results. It is possible that the condition is due to a sensitisation to some bacterial protein, as foods and drugs seem to play no part in its etiology.

ERYTHEMA NODOSUM

Whilst erythema nodosum is often classified as a form of E. multiforme, the uniformity of the lesions and its clinical course point to its being a clinical entity. From its association with rheumatic symptoms, E. nodosum was for long considered to be a rheumatic affection, but more recent reports point to its possible association with other diseases such as tuberculosis, syphilis, etc. It has been suggested that it is—

1. An acute specific fever.
2. An infection with the micrococcus rheumaticus.

3. A manifestation of tuberculosis.
4. A manifestation of syphilis.
5. Due to drugs.
6. A sensitisation to a fungus such as ringworm.

1. E. Nodosum as an Acute Specific Infection

Symes has recently discussed the question and strongly upholds this theory. In support of it he quotes the facts that the disease may be transferred from person to person and may occur in small localised outbreaks and in epidemic waves. It also has a definite seasonal and a fairly constant age incidence. The systematic distribution of the rash, the tendency to relapses, and the conferment of immunity also support this view. **Anderson** and **Cooper** and others have also reported more than one case occurring in the same family or household.

Rosenow in 1915 excised lesions from cases of E. nodosum, emulsified them, and made cultures. From subcutaneous nodules he obtained a polymorphous, sometimes clubbed, often curved, barred diplo-bacillus. This same organism was isolated in pure culture from each of 6 cases of E. nodosum. He also isolated the same organism from a cervical gland draining an infected tonsil in a case of E. nodosum and from the circulating blood in pure culture in 2 cases of E. nodosum. In smears from the original colonies all grades from bacilli to diplococci were found. On artificial culture it became a definite bacillus. **Rosenow** thinks that it is one organism in different forms. Injected intravenously into dogs, rabbits, and guinea-pigs, it showed a striking affinity for the subcutaneous tissues, producing local subcutaneous hæmorrhagic inflammatory lesions with enlargement of the regional lymphatic glands. From these lesions the organism was repeatedly isolated. On artificial cultivation and on animal passage the affinity for the subcutaneous tissues disappears. By passage through animals its virulence increases, and it assumes the form of a streptococcus and acquires an affinity for the joints, muscles, fasciæ, and endocardium, producing hæmorrhages in the muscles and heart valves soon after injection, and later a non-suppurative arthritis, myositis, and endocarditis. **Rosenow** considers it the cause of E. nodosum,

and thinks that it explains the relation of E. nodosum to rheumatism, measles, diphtheria, scarlet fever, and tuberculosis. These diseases afford it a focus from which it may gain entrance into the blood stream. **Rosenow's** findings, however, have never been confirmed.

Emrys Roberts, from a case of E. nodosum in a soldier, isolated what he considered the bacillus influenza from the blood; and **Neave** found a streptococcus in the blood of another case.

Perigal, Pollock, and **Joint** all report cases of E. nodosum within a few days after measles, and **Craig** reports 1 case in a child peeling from scarlet fever. **Joint** saw 9 cases of E. nodosum in 300 cases of measles, and concluded that he was dealing with 2 diseases both occurring in epidemic form.

2. E. Nodosum and Rheumatism

The association of joint pains and occasionally of endocarditis has lead many to support the rheumatic theory. Using the word rheumatism in the sense of an infection with the micrococcus rheumaticus, there is no evidence to support the rheumatic theory except the clinical observations. The fact that salicylates help in the treatment is no proof of a rheumatic origin. It is quite possible that an organism such as **Rosenow** described might produce endocarditis, pleurisy, arthritis, etc. If E. nodosum were a true rheumatic condition, one would expect it to occur frequently as a complication in rheumatic fever, and that is not the case.

3. E. Nodosum and Tuberculosis

Within recent years a great many writers have drawn attention to the frequent association of E. nodosum with tuberculosis. Numerous cases like that reported by **Meara** and **Goodridge** have been recorded. This case of E. nodosum developed tuberculous meningitis soon afterwards, and the post-mortem examination showed tuberculosis of the meninges and lungs. Similar cases have been reported by **Ochme** and others. The other type of case is where the patient with a recrudescence of an old tuberculosis develops E. nodosum. Such cases have been reported by **Ward** and others.

Courmant, Savy and **Charlet, Pic** and **Alamartine** did

agglutination tests for tuberculosis in E. nodosum, and always obtained positive results. **Pollak, Calderola,** and others found the tuberculin Pirquet reaction to be positive in cases of E. nodosum, but considering the frequency of positive reactions in all individuals, no great stress can be laid on these findings. **Troisier** and **Marfan** gave intradermic injections of tuberculin and obtained nodules resembling those of E. nodosum. **Marfan,** however, considered that the nodules were less elevated, their limits less marked, and their course shorter than in true E. nodosum. **Thibièrge** and **Gastinel** also produced lesions like E. nodosum by injection of tuberculin, but in the same patients they obtained identical lesions by injections of antidiphtheritic and antitetanic serum and also by injections of salt water. **Alamartine** quotes the experiments of **Gougerot** and **Laroche** who, by inoculation of tubercle bacilli into animals, produced cutaneous tuberculides which corresponded both macro- and microscopically with lesions of E. nodosum. **Landowzy, Laederich** and **Richet** report a case of typical E. nodosum with endocarditis and congestion of the apex of the right lung. In an excised nodule they found the tubercle bacillus, and guinea-pigs inoculated from the nodule died of tuberculosis. **Gutmann** also demonstrated the tubercle bacillus in the circulating blood and nodules in a case of E. nodosum. **Holland,** on the other hand, from 9 cases of erythema nodosum inoculated guinea-pigs with fresh nodes, and in all obtained negative results.

From all the above evidence therefore one must admit that there is a close connection between tuberculosis and E. nodosum. It may be in some cases a manifestation of actual tuberculosis in which the patient is sensitised to tubercle, and on a recurrence of the disease develops an acute lumpy tuberculide indistinguishable from E. nodosum. On the other hand, the two diseases may predispose to one another. Patients after an attack of E. nodosum may be specially susceptible to infection with E. nodosum. **Vetlesen**, in a recent discussion of the subject, " expresses no doubt as to the relationship of the two conditions, and has learnt to regard E. nodosum as a danger signal."

As in tuberculosis, so in leprosy, lesions like E. nodosum have been reported by **Hallopeau** and **Grandchamp.** In these cases they found no leprosy bacilli in the lesions, and think that the

lesions were due to toxines and that they were dealing with leprides and not with a double infection with E. nodosum and leprosy.

4. E. Nodosum and Syphilis

In 1896 **De Beurmann** and **Claude** reported cases of syphilis with lesions absolutely identical clinically with E. nodosum. They thought the lesions were due to the syphilis and were not a double infection. They pointed out that all intermediate forms occurred between E. nodosum and the typical gumma, and recommended that these lesions should be called nodose syphilides. **Hoffmann** also later recorded similar cases in the secondary stage of syphilis and agreed with **De Beurmann** and **Claude** that they were really nodose syphilides, which were due to a syphilitic phlebitis of the subcutaneous veins. **Stumpke** and **Chauffard** and **Le Conte**, however, think that these cases are double infections with E. nodosum and syphilis, as they differ from gummata in their evolution, benignity, and absence of ulceration. The spirochæta pallida could not be demonstrated in the lesions, and the patient may recover without antispecific treatment.

These cases, therefore, of E. nodosum occurring in the course of syphilis seem to be in the same position as the cases occurring in tuberculosis. Some of them may be true syphilitic lesions starting in the veins, and others may be double infections, the syphilis, like tuberculosis, predisposing to the infection.

5. E. Nodosum from Drugs

Fordyce, Schidachi, Thibièrge, Hallopeau and **Teisseire** and others have recorded cases with nodose lesions in the skin from taking iodides. Although the lesions resembled E. nodosum, in most cases they occurred on the front of the thighs and not over the shins. They were undoubtedly due to the drug and show how closely all nodose lesions, from whatever the cause, may resemble E. nodosum.

6. E. Nodosum and Ringworm

Acute nodular lesions indistinguishable from E. nodosum have been described in cases of kerion ringworm. It will be

shown later (p. 157) that these lesions are due to the blood infection with the ringworm fungus in a sensitised person.

Blood Changes in E. Nodosum

Blood examinations were made by **Hoyer** in 20 cases of E. nodosum. He found little change in the red blood-cells apart from a slight reduction in their number in about two-thirds of his cases. In most cases the total number of leucocytes was above normal at the time of the eruption, and as this faded the number returned to normal. Early in the disease there was a neutrophilia, eosinophilia, monocytosis, and lymphocytosis. As the eruption faded numerous neutrophiles with rod-shaped nuclei appeared and persisted for a considerable time. The author points out that these changes do not suggest a rheumatic condition, but are more like those of anaphylaxis.

Conclusions regarding E. Nodosum

1. The older conception of E. nodosum as a rheumatic condition must be revised.

2. The cases described in the literature may be divided into two groups :

(1) True E. nodosum.
(2) False E. nodosum.

3. True E. nodosum is probably due to infection with a definite organism such as that described by **Rosenow.** The distribution of the lesions and the clinical course are very constant. The disease seems to be infectious, as it may occur in small epidemics. The skin lesions are to be looked upon as sensitisation phenomena due to the same mechanism as the skin rashes of the exanthemata. The deep nodose character of the eruption is due to its starting from a subcutaneous vein. Tubercle and syphilis, on the one hand, seem to predispose to infection with E. nodosum, and, on the other hand, E. nodosum seems to predispose to infection with tubercle.

4. False E. nodosum is the eruption which may occur in tuberculosis, syphilis, leprosy, and ringworm. The nodes are to be considered as sensitisation phenomena, and would be better

called acute nodose tuberculides, syphilides, leprides, trichophytides, or microsporides. To the above group also belongs the nodose eruption which sometimes follows the administration of iodides.

5. Both the true and false E. nodosum are sensitisation phenomena, a different antigen being responsible in each group of cases, but the skin reaction is similar, if not identical in all. In both groups of cases the lesion centres round a subcutaneous vein, hence the similarity in the appearance of the nodes.

6. At present there seems to be no method by which the true and the false cases can be distinguished with certainty. If the causes which operate in false E. nodosum can be excluded, then one concludes that the eruption is one of true E. nodosum.

PURPURA

It is customary to divide the purpuras into two groups:

(*a*) *Primary* or *Idiopathic*, where the purpuric rash is the only or chief feature; and

(*b*) *Secondary* or *Symptomatic*, where the eruption occurs in the course of some definite infection or poisoning.

The *primary purpuras* are usually divided into—

1. Purpura simplex.
2. Purpura hæmorrhagica (**Werlhoff's** disease).
3. Purpura rheumatica, peliosis rheumatica (**Schönlein's** disease).
4. **Henoch's** purpura.

The *secondary purpuras* may occur in association with—

1. The exanthemata, such as scarlet fever, smallpox, etc.
2. Other general infections, such as septicæmia, pyæmia, malaria, syphilis, general tuberculosis, etc.
3. Diseases of the blood, such as leucocythæmia, hæmophilia, etc.
4. Toxæmias, such as malignant disease, disease of viscera, specially the liver and kidneys, etc.
5. Drugs such as potassium iodide, quinine, chloral, etc.
6. Serum disease.

The secondary purpuras need not be specially discussed. Their etiology is that of the condition which causes them plus

some other factor. Some of them are anaphylactic, such as those due to serum disease; others are generally admitted to be due to toxines which act by injuring the endothelium of the blood-vessels.

The primary purpuras, however, require some discussion. They are closely allied to the erythemata, and as in peliosis rheumatica, may occur together with an erythematous eruption. It is known that in purpura there is a marked diminution in the number of blood platelets. **Hess** thinks this is due to a destruction of the platelets, and that the platelet substance is in solution in the serum. He bases this opinion on the fact that, if normal blood is centrifugalised for 2 hours so as to remove the platelets, the coagulation time is greatly prolonged, whereas in purpuric blood the coagulation time is but little affected by centrifugalisation.

In 1914, **Ledingham** produced experimental purpura in animals. He found that an anti-guinea-pig platelet serum was toxic for the guinea-pig and produced in it a condition which closely resembled purpura hæmorrhagica in man. Later, **Ledingham** and **Bedson** showed that anti-red-cell and anti-white-cell sera did not produce purpura. It could only be produced by an anti-platelet serum. In the animals in which purpura was produced, a marked fall in the number of blood platelets was found. These findings have been confirmed by **Neisser** and **Krumbhaar, Lee** and **Robertson, Gottlieb** and **Watabiki. Bedson** in 1921 showed that anti-platelet serum contains a specific antibody for platelets, and in 1922 he found that a reduction in the number of platelets alone is insufficient to bring about purpura. The intravenous injection of peptone or agar serum, both of which cause a diminution of blood platelets, fails to produce purpura. The other factor which he considers necessary is a degeneration of the blood-vessel endothelium due to some toxine. In support of this is the fact that, if the endothelium of the vessels in a young rabbit be injured by the intravenous injection of anti-rabbit-red-cell serum and the platelets subsequently removed from the circulation by the introduction of agar serum, purpura is produced. From these experiments, therefore, it would seem that, in purpura, injury to the endothelium of the vessels, together with diminution of the blood platelets, are the essential factors.

As to whether purpura is anaphylactic in nature there is not much direct evidence on which to base an opinion. If one assumes that in serum sickness the endothelial cell is sensitised, the circulation of the antigen would produce a reaction in and injury to the endothelial cell. If the blood platelets are not destroyed then the ordinary erythematous or urticarial rash would result, but if the blood platelets were destroyed then the rash would be purpuric in character. Similarly, a purpuric rash might be produced by any toxic substance which destroys the blood platelets and injures the endothelium. This might account for hæmorrhagic rashes from drugs, snake bites, etc. The purpuras such as **Heroch's** purpura, where visceral lesions occur, are probably similar to the cases of E. multiforme with visceral lesions, with the additional factor of toxic injury to the endothelium of the vessels.

Dixon recently reports very good results in the treatment of purpura hæmorrhagica by injection of blood from one or other of the parents of the patients. **Wilson** also recently recorded a case of **Henoch's** purpura in a child who recovered rapidly after 3 injections of his father's blood serum. **Linser** also reports good results in 2 cases. This human-serum treatment might cause benefit by the introduction of fresh blood platelets, but **Nobecourt** and **Tixier** obtained good results in the treatment of purpura by injections of **Witte's** peptone. This last observation, although an isolated one, supports the sensitisation theory of the origin of purpura.

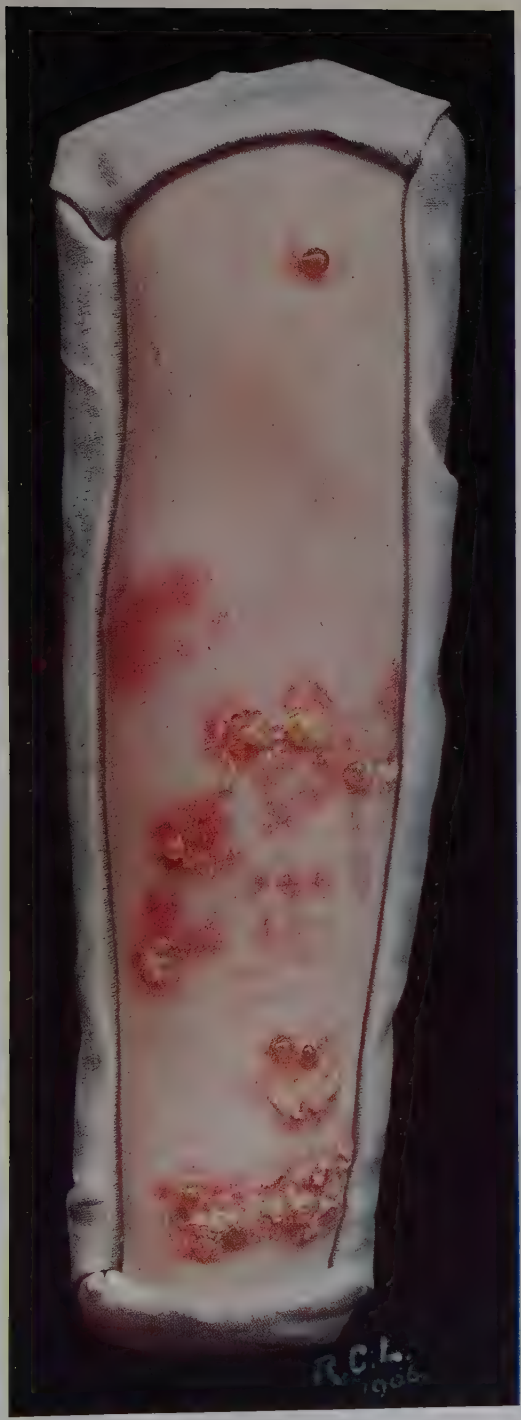
CHAPTER VI

DERMATITIS HERPETIFORMIS AND PEMPHIGUS

Dermatitis herpetiformis is a disease which is allied in many ways to the urticarias, the erythemata, and the pemphigus group. The generally accepted view about D. herpetiformis is that it is a toxæmia probably from a bowel absorption, but as yet the exact nature of the toxine is undecided. The nature of the eruption, however, would suggest that it is a sensitisation phenomenon, probably of intestinal bacterial origin. The periodicity of the attacks of eruption also suggest periods of sensitiveness, alternating with periods of temporary desensitisation. The intense itching and the grouping of the eruption suggests a sensitisation of the nerve endings or peripheral nerves from which the reaction which causes the skin eruption arises, and if one assumes this, it explains the difference between the eruption in urticaria and D. herpetiformis. In the former the endothelial cells of the skin vessels are sensitised, and in the latter the nerve endings.

The almost constant and very marked eosinophilia in the blood is another point greatly in favour of the sensitisation theory. The good results obtained by auto-serum therapy also point in the same direction. **Corlett, Fordyce, Howard Fox, Gottheil, Heidingsfeld, Lowingberg,** and **Heuck** all report marked improvement in D. herpetiformis from auto-serum treatment. **Linser** also reports a very good result in a case of dermatitis herpetiformis in a pregnant woman (herpes gestationis) from injections of serum from healthy pregnant women. **Lux** and **Ullmann,** however, found no benefit from auto-serum therapy in D. herpetiformis.

The presence of indicanuria in D. herpetiformis points to an intestinal absorption, and **Calvé** has shown that indol and



DERMATITIS HERPETIFORMIS.

skatol, which are produced by intestinal fermentation, if injected into rabbits, produce symptoms like those of anaphylactic shock, and the blood shows a "crise hémoclastique" with a leucopenia, and œdematous infiltrations of the internal organs occur. This change, he claims, is the same as that produced by protein shock. Therefore he considers D. herpetiformis to be a disease due to shock from absorption of indol and skatol.

So far as I can find, there are no records of cutaneous food tests having been done in D. herpetiformis. I tested 1 case to several foods, but with negative result.

The fact that arsenic so often acts beneficially in D. herpetiformis suggests that the nervous system is implicated in this disease. Starvation treatment and drinking large quantities of water have also been found to be very successful in bad cases. Presumably that is due to the dilution of toxines absorbed from the bowel. Intestinal antiseptics such as salol, calomel, etc., probably also act by diminishing intestinal fermentation.

I think, therefore, that we may conclude that D. herpetiformis is probably due to sensitisation of groups of cutaneous nerve endings to some bacterial protein from the bowel. Definite foods, such as eggs, have occasionally produced the eruption, but that is the exception. Meat proteins, however, possibly produce a suitable intestinal pabulum on which bacteria flourish. The effect of dieting, intestinal treatment, and the presence of indicanuria, point to the intestine being the source of absorption. The blood eosinophilia and the success of auto-serum therapy favour the sensitisation theory. The periodicity of the attacks, with intervals of comparative freedom from eruption, also point in the same direction, and after months or years the patient passes from the sensitive condition on to complete immunity.

PEMPHIGUS

The acute pemphigus of the new born and butcher's pemphigus are not included in this group. They are definite organismal infections. Pemphigus vulgaris or chronicus, P. foliaceus, and P. vegetans form a group which is very closely allied to D. herpetiformis, and much that applies to the latter disease also applies to the former. There is the same eosinophilia, and auto-serum

therapy also has given good results in some cases of pemphigus. **Fischer, Linser, Winfield, Praetorius,** and **Heuck** all report improvement, and in some cases cure, after auto-serum treatment. **Gottheil** and **Satenstein** in 2 cases obtained no result, but these cases were probably too far advanced for any form of treatment to be effective.

Tominasi in 1918 reports the result of the examination of 5 cases of P. vulgaris and 2 of P. vegetans. Blood cultures in all 7 cases were negative. From the vegetations in both cases of P. vegetans, and from the internal organs of 2 cases of P. vulgaris which died, he isolated an organism identical with that first described by **Radaeli** in 1906. It is a motile bacillus with club-shaped swellings at each end. It is Gram-negative and a facultative anærobe. Complement fixation tests were made, using this organism as antigen, and 2 out of 4 cases gave a slight positive result.

Tominasi's results agree very closely with those previously published by **Radaeli, Pasini,** and **Copelli**. Out of 19 cases which have been examined post-mortem and cultures made, the same organism has been found in all. The organism is found in the heart, spleen, and liver, where it may be a mixed infection, but a pure culture has always been obtained from the bone marrow. Further work, however, is necessary before concluding that the above organism is the cause of pemphigus.

The type of the eruption, the presence of a blood eosinophilia, the periodicity of attacks of eruption, the good effect of arsenic internally, and of auto-serum therapy link the cases of pemphigus to D. herpetiformis, and probably the same mechanism is responsible for both groups of diseases. Pemphigus is a much more serious disease than D. herpetiformis, and it is possible that in the latter the infection is localised in the bowel, and by absorption from the bowel the eruption, etc., are produced; whereas in the former there may be an additional general infection of the blood and internal organs with the organism. That would account for the temperature which is so often present in pemphigus and for the fatal result.

Pemphigus foliaceus may begin as an ordinary P. chronicus or D. herpetiformis, and only develop the foliaceus eruption later. In all the cases I have seen the Bac. pyocyaneus was

PEMPHIGUS FOLIACEUS.

obtained in pure culture from the skin. This would seem to indicate that P. foliaceus is due to the same cause as D. herpetiformis or P. vulgaris, together with a superadded infection with Bac. pyocyaneus.

Pemphigus vegetans also begins like P. vulgaris, and later develops vegetating lesions. This would point to its being due to the same cause as P. vulgaris with a superadded infection, with an organism which produces the warty vegetating lesions.

CHAPTER VII

SENSITISATION IN TUBERCULOSIS

That a true sensitisation occurs in tuberculosis is now generally admitted, so that it will be sufficient to mention the various hypersensitive reactions which occur and discuss their significance.

LOCAL, FOCAL, AND GENERAL REACTIONS

When a patient suffering from tuberculosis is given a suitable subcutaneous injection of old tuberculin, within 24 hours a local reaction occurs at the seat of the inoculation. This is known as the *local* or "*Stich*" *reaction*, and indicates that the patient is sensitised to tuberculin, but gives no indication as to the seat of the lesion. The duration and the severity of the reaction depend on the degree of sensitiveness of the patient.

By absorption of the tuberculin a general reaction may occur, with a rise of temperature, headache, malaise, etc. This is the *general reaction*, and again does not indicate the seat of the lesion.

A *focal reaction* may also occur in all foci of tuberculosis in the body wherever they may be situated. If in the skin or subcutaneous tissues, this reaction is shown by redness and swelling of the lesion for some days. This reaction is of great value in diagnosis, and for practical purposes may be considered as diagnostic of tubercle. If the dose of tuberculin be large and the reaction severe it may lead to a breaking-down of the lesion and a spread of the disease. This occurred frequently in the early days of the use of tuberculin for treatment, and did much to check the use of tuberculin for that purpose. But with the smaller doses which are now generally employed the mild focal reaction is usually harmless, if not in some cases beneficial. The newer preparations of tuberculin, however, in suitable

doses, do not give rise to marked reactions, but a discussion of these is outside the scope of the work.

The phenomena of sensitisation occur in practically all forms of tuberculosis, but in the late cachectic stage of the disease, when the protective mechanism has broken down, they disappear. As would be expected, a complement fixation reaction analogous to the **Wassermann** reaction in syphilis occurs in tubercle. Many have worked at this subject. The most recent article is by **Nimmo Smith,** who concludes that, where the **Wassermann** is negative, a positive tubercle complement fixation reaction is strong presumptive evidence of tuberculosis, and that, in a clinically tuberculous patient, a positive reaction denotes activity of the lesion. The reaction disappears in far-advanced cases. The specificity of the reaction is doubted by many. **Nimmo Smith** states that non-specific fixations may occur, notably when the serum gives a positive **Wassermann** reaction. Conversely, several workers have recorded positive **Wassermann** reactions in tuberculides, etc., where there was absolutely no evidence of syphilis. This question of the specificity of the tubercle complement fixation reaction is still in doubt, some, like **Milian,** holding that tubercle may give a positive **Wassermann,** whilst others, like **Tzanck** and **Pelbris,** that cases of tuberculosis giving positive **Wassermann** reactions are really cases of tubercle with latent syphilis. The sera of patients with tuberculosis have also been shown by **Arloing** and others to give positive agglutination tests to the tubercle bacillus.

Passive sensitisation to tubercle has also been successfully achieved by **Bauer, Helmholz,** and others by injecting the serum of tuberculous guinea-pigs and tuberculous patients into normal guinea-pigs.

Human beings and animals cannot be sensitised to tubercle by injections of tuberculin. In order to obtain sensitisation with all the skin and other reactions, the individual must be actually infected with tuberculosis.

CUTANEOUS REACTIONS

The most widely used test is the *Von Pirquet reaction.* The test is done by making a small scarification on the arm, short of

drawing blood, and rubbing a 25 per cent. solution of old tuberculin gently into the area. In 24 hours an area of erythema surrounds the scarified area, which is raised up into a papule in the centre (Plate opposite). A well-marked reaction lasts 4–5 days and then slowly fades. Severe reactions may lead to pustulation or necrosis in the centre. The reaction may also be delayed and only appear after 4 or 5 days.

THE VALUE OF THE VON PIRQUET REACTION

In 1909 I applied the **Pirquet** test to 75 cases of skin diseases in adults, 12 cases of lupus vulgaris, 1 of tuberculous ulceration of the skin, and 3 cases of tuberculides. All gave positive reactions. Cases of lupus erythematosus, dermatitis, psoriasis, erythema multiforme, rodent ulcer, favus, D. herpetiformis, pityriasis rubra pilaris, acne, tertiary syphilis, and prurigo gave positive reactions. In the 75 cases, which included 16 of tuberculosis, 40 (53 per cent.) gave positive reactions. Very similar results have been obtained by many others, so that it is safe to say that a considerable percentage (over 50 per cent.) of apparently non-tuberculous individuals and practically all cases of tuberculosis will give positive reactions. A positive reaction is, therefore, of no value in the diagnosis of a doubtful lesion. A negative reaction, however, especially if repeated, is of great value, as for practical purposes it may be considered to exclude tuberculosis. In young children the test is in rather a different position from what it is in adults. They have been more recently infected, and a positive reaction is of more value. **Bondy**, in 1908, examined 350 new-born children in the first 4 days of life and did not find a single positive reaction, although 71 per cent. of their mothers reacted positively. He also quotes **Pirquet** who tested 147 new-born children, **Prouff** 54, and **Feer** 70 new-born children. Among these 271 children not one gave a positive reaction. **Langstein** saw 1 positive reaction in 100 infants, and **Bauer** 6 in 48 infants. Therefore it may be taken that new-born children very seldom react positively. This may either be due to their not yet having been infected with tubercle, or it may be due to a special non-sensitiveness of the skin of the new born. The following

Luetin Reaction.

Upper = Intracutaneous (positive).
Middle = Cutaneous (negative).
Lower = Control.

Von Pirquet's Tuberculin Reactions.

Upper = Human Tuberculin.
Middle = Control.
Lower = Bovine Tuberculin.

are some of the figures given by various authors for older children :—

Cattermole .	38 per cent.	positive in	66	children tested.
Fishberg . .	52 ,,	,, ,,	588	,, ,,
Kerpetz . .	53 ,,	,, ,,	276	,, ,,
Salvetti . .	26 ,,	,, ,,	630	,, ,,
Veeder and **Johnston** . .	44 ,,	,, ,,	1321	,, ,,

Pirquet tested the value of the reaction in 100 cases which died later and were examined post-mortem, and found that in only 1 case was the reaction positive where at the post-mortem examination no macroscopic tuberculosis could be demonstrated.

The severity of the reaction is not a very good index of the severity of the infection. In latent tubercle, as a rule, the reaction is not very marked, but if any extension of the disease occurs, the reaction becomes stronger. It is well known that for some time after measles a Pirquet reaction which was previously positive will become negative. This probably means that an attack of a disease such as measles temporarily destroys the antibodies to tubercle. It also explains the common clinical observation that multiple spots of lupus vulgaris are very apt to occur after measles when the resistance to tubercle is absent. A similar disappearance of the skin reaction to trichophytin in fevers will be referred to later on. Therefore it may be assumed that except after diseases such as measles a positive Pirquet's reaction may be taken as a sure sign of infection with tuberculosis.

Colliver did experiments to see whether the skin of one part of the body was more susceptible than any other. He tested 50 children on the dorsum of the hand and foot, inside of the knee, and on the shoulder, the neck, the back, and on the ulnar side of the forearm, and found no difference in the reactions. Therefore he concludes that there is no good reason for making the Pirquet test elsewhere than on the arm, which has the advantage of being convenient.

Mondolfo and **Coscera** performed the test on the arm and also near the seat of the tuberculous lesion, and found in 82 cases that in the great majority both reactions were positive or negative at the same time, although the regional reaction was

the more intense. It was rare for the regional reaction to be positive and reaction on the arm negative, whilst the converse never occurred. **Mondolfo** and **Coscera** also quote **Pollitzer** as obtaining similar results.

A great many observers have obtained negative Pirquet tests in advanced tuberculosis or in acute general tuberculosis. This is generally attributed to the breaking down of the protective mechanism in the late stages of the disease, but **M'Neil** has shown recently that, by a more careful technique by scratching the epithelium well off the surface of the skin and using undiluted tuberculin instead of a 25 per cent. or 50 per cent. solution, positive reactions may be obtained within a few days before death from miliary tuberculosis.

Bouveyron compared Pirquet reactions from tuberculin with those produced by the addition of certain drugs. He found that the addition of adrenalin to the tuberculin increased the severity of the reaction, whereas the addition of quinine, antipyrin, or pyramidon diminished the reaction. The administration of adrenalin to patients suffering from a tuberculous fever rendered the skin more sensitive to tuberculin, whereas the administration of quinine, antipyrin, or pyramidon had the opposite effect.

THE INTRACUTANEOUS TUBERCULIN TEST

This method is not used so extensively as the cutaneous. It is rather more difficult to perform and the results are not so easy to interpret. **Bass** and others report that it is more sensitive than the Pirquet and, like the trichophytin tests, to be referred to later, is almost too sensitive. **Monte** recommends it as an additional test in cases where the Pirquet is negative.

Kolmer, Immerman, Matsunami, and **Montgomery** found that cutaneous and intracutaneous reactions to tuberculin among persons reacting positively to both were rendered more extensive by the administration of potassium iodide and potassium bromide. This is similar to the effect of iodides and bromides on the luetin test to be referred to later. **Solis-Cohen** found that the intracutaneous test can be done with T.R. just as well as with O.T. **Debré** and **Bonnet**, by experiments on guinea-pigs, have shown that the reaction to tuberculin introduced intradermically into guinea-

pigs infected with living tubercle bacilli, varies more or less directly with the resistance of the animal. They found that in the heavier animals infected with tubercle, the health remains good till just shortly before death, whereas in the lighter ones there is a progressive loss of weight almost from the start. After death the heavier guinea-pigs are found to have a local lesion at the seat of inoculation, in process of cure with infection of lymphatic glands, large tubercles in liver and spleen, and tuberculous broncho-pneumonia, and in the lighter animals there is very little local lesion at the seat of inoculation and a general tuberculosis throughout the body. If intradermal tests are done on infected guinea-pigs, they vary directly in intensity with the weight of the animal, and the reaction is present for a much longer time the heavier the animal.

These results are similar to those found in human infants. In weakly, poorly nourished children tuberculosis is accompanied by a progressive loss of weight and early failure to respond to the tuberculin test, whilst in better nourished infants the tuberculin reaction persists almost up to the time of death.

Brisacca, basing his work on the fact that it has been shown that tuberculous persons are hypersensitive to normal horse serum, did a series of intracutaneous tests with horse serum. In 119 cases of cutaneous tuberculosis he found that 80 per cent. reacted positively, and 3 cases of pulmonary tuberculosis all gave positive reactions. The reaction was more marked in the early than in the advanced stages of the disease, in active than in torpid cases, and in localised than in diffuse infections. He claims the superiority of the test over the Pirquet test in that it is only positive when the disease is fully developed.

THE "MORO" REACTION

This reaction is obtained by rubbing into the skin an ointment consisting of equal parts of old tuberculin and anhydrous lanolin. The ointment is usually rubbed into the side of the chest or abdomen. About 1 gr. of the ointment is used. In 24–48 hours several small red papules appear on an erythematous base, and in more severe reactions the papules are larger, the erythema more marked, and itching is present. The lesions persist for

3–7 days and gradually fade, leaving slight pigmentation. This test has very much the same significance as the Pirquet test and has the additional advantage of giving fewer positive reactions in apparently healthy individuals, but, according to **Emmerich**, it disappears earlier in progressing tuberculosis than the Pirquet reaction.

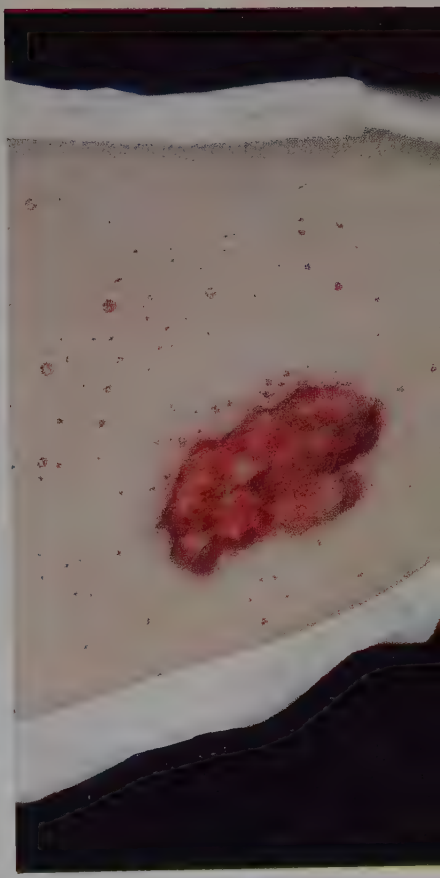
In 1908, **Moro** did some interesting experiments with this ointment, comparing it with the effect of pure lanolin. After rubbing one arm of a tuberculous patient with tuberculin ointment and the corresponding spot on the other arm with pure lanolin, he obtained characteristic reactions on both arms. This he explains as a reflex nervous influence on the vaso-motor mechanism of the skin, and describes it as a specific nervous "allergy."

For a number of years Moro's ointment has been used in the Skin Department of the Royal Infirmary both for diagnosis and treatment. In doubtful skin lesions where tuberculosis is suggested, the application of Moro's ointment on lint, freshly applied night and morning for 3 or 4 days, causes a severe local reaction, with swelling of the lesion and an area of erythema around it. The lesion may also slough in places and ulcerate. In tertiary specific lesions either no reaction occurs or a very slight reaction due to a tuberculous focus elsewhere. A number of cases of lupus vulgaris were also treated some years ago by applying the tuberculin ointment for several days till a marked reaction was produced. The tubercle nodules ulcerated and sloughed out. The lesion was dressed with a simple zinc paste till it healed over. The results were rather disappointing, but better results were obtained when pure carbolic acid was applied to each sloughed nodule when the reaction was at its height. One drawback to the method is the sickening smell produced in the ulcerated areas. This is very objectionable to the patient when lesions on the nose are treated by the above method.

Recently daily inunction of different areas of skin with tuberculin ointment, as suggested by **Sir Robert Philip**, has been used with considerable success in the treatment of gland and other forms of tuberculosis.

The mechanism of these different tuberculin skin reactions will be discussed later under cutaneous reactions.

1



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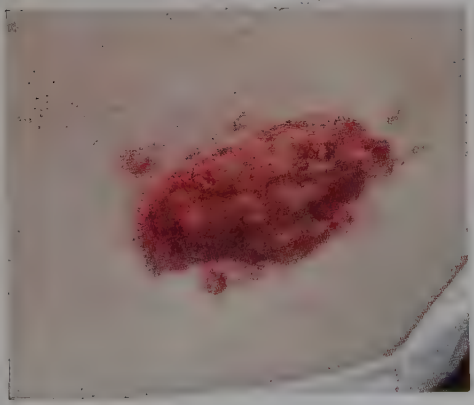

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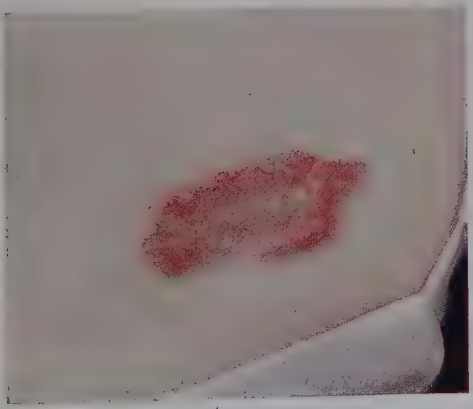


4

5

LUPUS.

1. Small Patch of Lupus on Thigh.
2. ,, after application of 5 % Old Tuberculin Ointment for 6 days.
3. ,, ,, ,, ,, ,, 12 days.
4. ,, ,, ,, ,, ,, 2 months.
   2 years.

very satisfactory results, and states that the results were always negative in the control cases even when syphilis was present.

TUBERCULOSIS OF THE SKIN

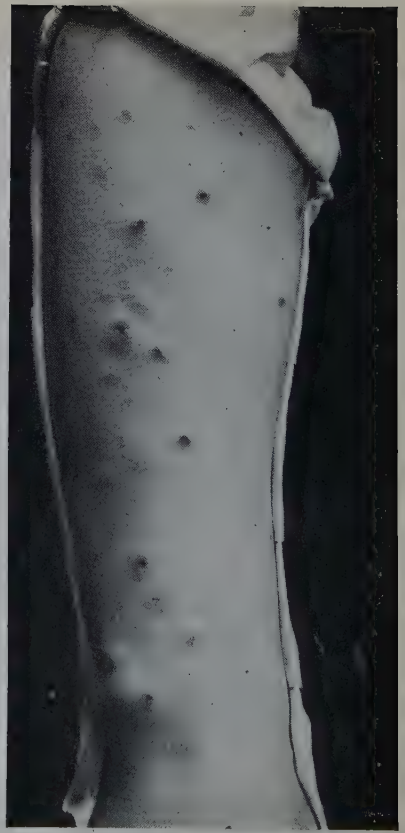
Tuberculous infections of the skin may be lupus vulgaris, tuberculosis cutis verrucosa, or scrofuloderma. The lesions are all essentially the same, and the different varieties depend on the method and situation of infection. In tubercle of the skin, as in all forms of tuberculosis, sensitisation occurs as is evidenced by a positive skin reaction. It is rather astonishing how little inflammatory reaction is often present round the nodules in lupus vulgaris. Possibly this is due to the tubercle bacillus being so well hemmed in by giant, epithelioid, and other cells, and also to the absence of blood-vessels in the nodules. As already mentioned, multiple lupus vulgaris lesions almost invariably occur after measles, because the body loses its resisting power temporarily and the absence of the tuberculin skin reaction prevents any reaction occurring between the skin and the tubercle bacillus, and therefore an infection with tubercle, in which the bacillus survives, occurs, and not a tuberculide in which the bacillus is destroyed. Similarly, in advanced cases of tubercle, disseminated miliary tubercle of the skin may occur, and here again the absence of a skin reaction allows the organism to grow in the skin, and a tuberculosis, and not a tuberculide, results.

The focal reactions in skin tuberculosis from injections of old tuberculin and from the external application of tuberculin have already been referred to. They are signs of a true sensitisation to tubercle. The improvement which sometimes occurs in lupus from a course of tuberculin injections shows that by this means the resistance can be raised to the infection, but as this question is more closely related to immunity than sensitisation, it is sufficient merely to mention the fact.

TUBERCULIDES

Tuberculides are the skin eruptions which occur as the result of a blood infection with the tubercle bacillus in persons who are sensitised to tuberculosis. They may be divided into three main groups :

Papulo-Pustular Tuberculide (Lichen Scrofulosorum).



Papulo-Necrotic Tuberculide.

1. Lichen scrofulosorum;
2. Papulo-necrotic tuberculide; and
3. Erythema induratum scrofulosorum (**Bazin's** disease).

The first two are essentially similar and will be grouped together. Erythema induratum is somewhat different and will be dealt with separately. As the etiology and pathology of these lesions are well known, it will be sufficient to state the views generally held now with regard to them, without quoting authorities.

LICHEN SCROFULOSORUM AND PAPULO-NECROTIC TUBERCULIDES

These tuberculides occur in individuals who have a small focal lesion of tubercle and in whom the bacillus has gained access to the circulation. The tubercle bacilli are carried to the skin capillaries and a local reaction occurs in the skin where they lodge. This reaction is essentially the same as the Pirquet reaction, but from the blood side instead of from the exterior. The older view that they were due to tubercle toxines has now been disproved, as the bacillus has been shown by numerous workers to be present, and the earlier the lesion is examined the more likely is it to be found. The reaction which occurs between the tissues and the bacillus results in a destruction of the bacillus, so that the lesion heals with or without a scar and no infection of the skin remains. The reaction, therefore, is a protective one. Microscopically, the tuberculides show the same structure as all tubercle lesions, with giant cells, epithelioid cells, plasma cells, etc. After injections of old tuberculin a general rash may occur all over the body. This rash is identical clinically and microscopically with lichen scrofulosorum, and in many cases, if not all, is a reawakening of a previous lichen scrofulosorum which had disappeared.

The papulo-necrotic tuberculides are not usually so extensive as lichen scrofulosorum and have been described under numerous names. The following are some of the names given to papulo-necrotic tuberculides occurring often in special situations, such as on the face, viz. acnitis (**Barthélemy**), disseminated follicular lupus (**Fox**), acne telangiectodes (**Kaposi**), acne agminata (**Crocker**), folliclis (**Barthélemy**), dermatitis nodularis necrotica

(**Hutchinson, Boeck**), hydrosandenitis destruens suppurativa (**Pollitzer, Dubreuihl**), toxituberculides (**Hallopeau**), paratuberculoses, necrotic granuloma (**Johnston**), acne scrofulosorum and acne cachecticorum (**Hebra**). It is also a question whether some of the cases of acne varioliformis are not cases of tuberculides.

Some workers have suggested that as the tubercle bacillus is present in tuberculides they should be called tuberculosis lichenoides, etc., but as they correspond to the syphilides, trichophytides, etc., there seems no good reason why the name should be changed, so long as it is borne in mind that the lesions are due to the presence of the bacillus and not to toxines only. **Wise** thinks that the various forms and types of eruption depend on—

1. The individual disposition of the patient;
2. The number of bacilli circulating; and
3. The degree of immunity reaction residing in the affected individual.

So far as I can find, **Gougerot** and **Laroche** are the only workers who have succeeded in producing tuberculides experimentally in animals. Unlike other workers they did not scarify the skin, but they pulled out the hair of the animal and rubbed in a culture of virulent tubercle bacilli. As a result, a papulo-necrotic tuberculide was usually produced, but sometimes lichen scrofulosorum and erythema induratum lesions. Microscopically and bacteriologically these lesions corresponded to tuberculides in man. They found that the occurrence of tuberculides was hastened if the guinea-pig was previously sensitised by tuberculin. They conclude from their experiments that a previous impregnation of the body with tubercle toxine is necessary for the production of tuberculides, and the severity of the reaction varies and so produces different types of tuberculide according as the bacillus is virulent, weakened, or dead.

ERYTHEMA INDURATUM SCROFULOSORUM (BAZIN'S DISEASE)

Erythema induratum is a much larger and more localised lesion than the other tuberculides. The lesion is a granuloma resembling tuberculous tissue commencing in association with

ERYTHEMA INDURATUM.

the deep veins of the skin. **Calcott Fox** and **Thibièrge,** and **Ravaut** produced tuberculosis in guinea-pigs by inoculating them with material from E. induratum lesions. I have seen a tubercle bacillus in pus from an ulcerated lesion. It is generally accepted now that the lesions are tuberculides where the patient is highly sensitised to the infection, and the resulting reaction between the bacillus and the tissues causes the lesion. It begins deeply in the skin, probably in a venule or arteriole, and this gives it its characteristic clinical appearance. It is analogous to the gumma in late syphilis. **Whitfield,** however, doubts whether all cases are tuberculous. He considers that the form in young girls is undoubtedly tuberculous, but in older persons one sees cases where the lesions microscopically do not have the tuberculous structure. In both cases the lesion originates in the deeper blood-vessels. The question of acute erythema induratum lesions has already been discussed under Erythema Nodosum.

OTHER SKIN LESIONS POSSIBLY RELATED TO TUBERCULOSIS

For a number of years a controversy waged over lupus erythematosus and its association with tuberculosis. There are still those who hold that it is a tuberculide, but the recent work of **Barber** and others has done much to clear matters up. Personally I do not think that lupus erythematosus has any connection with tubercle, except that the individual liable to it is also the type of person who is liable to tuberculosis. This matter will be further discussed under Lupus Erythematosus.

SARCOID TUMOURS

These include the sarcoid of **Darier-Roussy,** the multiple benign sarcoid of **Boeck,** Lupus pernio and lymphogranuloma benignum or **Steinberg's** lymphogranulomatosis. In all these conditions there occur indolent bluish-red nodules which somewhat resemble clinically and microscopically erythema induratum, although differing in their distribution from the latter disease. Opinions differ as to whether the above conditions are tuber-

culides or not. **Friebos, Sweitzer** and **Nichelson, Civatte** and **Vigne,** and others consider them to be true tuberculides, whilst **Bruhns** and **Alexander, Martenstein** and **Rejsek, Schaumann** and others hold an opposite view. Injections of tuberculin have been known to cause local reactions in sarcoids. The whole question of the sarcoids is still in doubt. Possibly some of the cases described as sarcoids are tuberculides, but it is by no means proved that all of them are of that nature.

EXFOLIATIVE ERYTHRODERMIAS

Acute lichen scrofulosorum lesions or injections of tuberculin may produce a scaly red rash, but a generalised exfoliative erythrodermia has been described by some authors as due to tuberculosis. **Bruusgaard's** case, associated with universal tuberculosis of glands in which the bacillus was found, seems to have been an example of this type of eruption, but in the majority of cases no history of or association with tuberculosis is to be found. It is possible that in such cases the rash is a sensitisation phenomenon due to sensitisation to the protein of some organism, which may be the tubercle bacillus in some cases, and in others some other organism or toxins. At present we have not sufficient information on which to make a definite statement.

It has also been suggested that parapsoriasis is a tuberculide. The same suggestion has also been made with regard to pityriasis rubra pilaris, but in both these conditions the evidence is inconclusive.

LICHEN NITIDUS

Pinkus showed that in lichen nitidus the structure of the nodules was that of a typical tubercle, and **Arndt** obtained a positive Pirquet reaction in one case, and in another case sections stained by **Much's** method showed 1 bacillus which looked like a tubercle bacillus. **Lewandowsky** had a case which showed no sign of tuberculosis clinically, but when the patient died 2 years later an active tuberculosis was found post-mortem. Another case developed a tuberculous pleurisy and lichen scrofulosorum. **Lewandowsky** considers lichen nitidus as a form of tuberculide. **Kyrle** and **M'Donagh** obtained a general

reaction to an injection of 1 mgrm. old tuberculin, but inoculations of guinea-pigs with pieces of the lesions were negative. Nevertheless they are inclined to support **Lewandowsky's** opinion. The most recent article on this subject is by **Zingale,** who summarises all the previously recorded cases (46). Of the cases reported, some showed no history of tuberculosis, others showed definitely its existence. He concludes that in all cases the cause is not the same, and that one can neither admit or exclude tuberculosis as a determining factor.

GRANULOMA ANNULARE

This condition has been described under a great many names, such as—

Erythema elevatum diutinum (**Crocker**), 1894.

Ringed eruption (**Calcott Fox**), 1895.

Eruption circinée chronique de la main (**Dubreuihl**), 1895.

Lichen annularis (**Galloway**), 1899.

Granuloma annulare (**Crocker**), 1902.

Tumores benigni sarcoidei cutis (**Rasch** and **Gregerson**), 1903, (**Galswsky**), 1908.

Erythemato-scleroses circinées du dos des mains (**Audry**), 1904.

Neoplasie nodulaire et circinée des extremités (**Brocq**), 1904.

Sclerose circinée des doigts (**Audry**), 1905.

Acanthoma annulare (**Leslie Roberts**), 1908.

Stereo-phlogose nodulaire et circinée (**Pellier**), 1910.

Celluloma annulare (**Pernet**).

It has been suggested that the above condition is a tuberculide allied to lichen nitidus and the sarcoids. **Graham Little,** in 49 cases, in only 4 could find a tuberculous history, and in only 1 was tuberculosis present. **Hudelo, Civatte,** and **Rubut** in 1920 report the cure of a case by tuberculin, but on the whole there is very little evidence to connect it with tuberculosis. *Angiokeratoma* has also been classified, especially by French dermatologists, as a tuberculide. It is a rare condition and occurs most commonly in tuberculous subjects. Apart from that there is nothing either in its clinical or histological appearance to connect it with tuberculosis. It is probably more closely associated

with chilblains than any other condition, and looks more like a congestion than an inflammatory phenomenon.

SUMMARY

1. That in tuberculosis a true bacterial sensitisation occurs is shown by the facts that:

(*a*) Local, focal, and general reactions occur on injection of tuberculin.

(*b*) Complement-fixing and agglutinating substances occur in the serum in cases of tuberculosis.

(*c*) Passive sensitisation can be produced.

(*d*) Cutaneous reactions to tuberculin—Pirquet reaction, Moro reaction, and intracutaneous reactions are present.

(*e*) Tuberculides occur in various forms in man, and have been produced experimentally in animals.

2. There is no definite proof that sarcoid tumours, exfoliating erythrodermias, lichen nitidus, granuloma annulare, or angiokeratoma are tuberculides.

CHAPTER VIII

SENSITISATION IN SYPHILIS

Syphilis resembles, in many ways, the acute specific fevers. After an incubation period of about 3 weeks the primary lesion develops. This primary lesion is a local focus from which a spread takes place by the lymphatic vessels to the glands, from which the spirochætes enter the circulation. As in the specific fevers, the explanation of the rashes in syphilis is based on the principles of sensitisation. Early in the infection, before there is any sign of the secondary rash, antibodies are present in the blood. This is demonstrated by the presence of a positive Wassermann reaction in the blood serum. These antibodies are brought by the circulation to the skin where they sensitise the cells, and the allergic reaction between the spirochætes and the skin leads to the production of the various secondary rashes. The incubation period between the primary and secondary stages represents the time it takes to sensitise the individual completely. At the end of 6 weeks the individual's skin is allergic and the spirochætes deposited in it through the circulation cause a reaction, which results in the roseolar rash. In this stage the individual is not very highly sensitised, and, therefore, the reaction is a comparatively slight one, but evidently sufficient to cause a destruction of the spirochætes in the skin. Later, if a further shower of spirochætes is sent out into the circulation, the individual being now more highly allergic, a larger rash occurs—papular, papulo-squamous, and later still nodular. Each of the secondary rashes becomes less and less extensive, and larger and larger in size. Finally, the tertiary stage is reached, where the allergy of the skin reaches its maximum and the large nodular gumma in localised areas results. All the evidence available goes to support the idea that in syphilis

one is dealing with a true bacterial sensitisation of the tissues, analogous in every way in the secondary stage to the specific fevers and to the sensitisation which occurs in diseases like tuberculosis. In the latter disease lichen scrofulosorum and the papulo-necrotic tuberculides correspond to the secondary syphilitic rashes and lesions in erythema induratum to the tertiary gumma. In discussing the question of sensitisation in syphilis one cannot avoid the question of immunity to syphilis. The numerous experiments of **Metchnikoff** and **Roux** and **Neisser** and his assistants showed that it is not possible to produce an active immunity to syphilis by subcutaneous or intraperitoneal injection of virus. It has long been recognised that an individual is only immune to syphilis so long as he still suffers from the disease, or only for a very short time after cure. The individual seems to be in the same condition, as will be referred to later under ringworm, where only a relative immunity is present. This so-called relative immunity is really a hypersensitiveness. **Ehrmann** and **Finger** and **Landsteiner** showed that attempts to reinoculate syphilis results in the production of a lesion of the same character as that from which the individual suffers. If the patient be in the secondary stage a series of papules result, and if in the tertiary stage a gummatous lesion develops : this raises the whole question of reinfection and superinfection. If superinfection occurs early enough before the individual is fully sensitised, a smaller lesion, resembling a primary, but with a slightly accelerated incubation period, is the result. As soon as the secondary or tertiary stage is reached any reinfection results in a lesion corresponding to the respective stages. Recently many cases have been reported in which within a few months after a definitely proved syphilitic infection an apparent reinfection with a lesion like a new hard chancre results. **Veress** and others think that these are not reinfections but early recurrences. They may occur on the site of the original chancre and cause the characteristic swelling of the glands so that they are indistinguishable from a real chancre, but they may occur on any part of the skin or mucous membrane and imitate an extragenital chancre. **Tomasczewski** refers to cases of reinfections reported in syphilitics by **Diday, Merkel, Kobner, Gascoyen,** and **Ducrey,** and considers that in all except **Ducrey's** case the lesions

were probably pseudo-chancres, *i.e.* gummatous lesions. **Neumann** and **Unna** showed that in clinically healed lesions a perivascular cell infiltration can be demonstrated, and they consider that the virus is still present, and that gummatous lesions on the seat of old primary lesions are the result of a local regrowth of the virus. In the cases of pseudo-chancres either due to a local regrowth of the virus or to reinoculation, the pseudo-chancre is not followed by a secondary rash. Within recent years, however, since treatment with arseno-benzol compounds came in, numerous cases have been recorded where a true reinfection probably occurred. In these cases the patient was cured of the disease, and the second infection ran a course the same as the first. In 1921, **Brown** and **Pearce** did a number of experiments by inoculating rabbits with syphilis and then treating them with salvarsan in doses insufficient to cure the infection. Such animals are highly susceptible to reinfection with syphilis. If this applies equally well to human beings, it suggests that treatment with drugs like salvarsan may cause an infection to revert to the condition in which the patient was when first infected before sensitisation had occurred, and thus a reinfection might occur whilst syphilitic lesions were still present from the first infection.

Nakano, in 1913, by injecting, into a case of congenital and one of tertiary syphilis, an extract of syphilitic organs or extracts of cultures of spirochæta pallida, produced swellings which broke down and ulcerated and left scars like gummata. From these results he concludes that in tertiary syphilis killed spirochætes and their toxines can produce gummatous lesions.

Experiments by **Neisser** to produce passive immunity to syphilis were all unsuccessful.

Cases of malignant syphilis, where large ulcerating lesions occur early in the infection, are probably not due to any special virulence of the virus but to the patient being very early and highly sensitised, so that excessive reactions occur wherever the spirochætes lodge. The well-known phenomenon of the rash in syphilis being made evident by administration of mercury is probably due to the mercury killing the spirochætes in the skin and liberating substances which cause the reaction. It is analogous to the positive Wassermann reaction which can be provoked by a dose of salvarsan.

It has been recognised for a long time that trauma has often a localising effect in the production of lesions in syphilis. In the secondary stage papules may appear at the seat of slight local irritation, such as the pressure of the clothes, and in the tertiary stage many cases of localised syphilitic lesions have been reported as the result of injuries, contusions, fractures, wounds, etc. Some think that these are due to the injury wakening into activity spirochætes which are already present. Spirochætes have been found in the skin, glands, bones, and mucous membranes in cases of latent syphilis where no visible lesions were present, and the injury might, by lowering the resistance of the tissues, cause these spirochætes to start to grow. **Pasini** in a recent article thinks that the trauma produces a fresh cellular infiltration with a lowering or absence of local immunity. The effect of traumata does not seem to have any association with sensitisation.

THE WASSERMANN REACTION

It is not proposed to enter into a discussion on the Wassermann reaction. The volume of literature on the subject is enormous. Although now admitted not to be a specific antigen-antibody reaction, it is sufficiently constant in the secondary and tertiary stages to be of use clinically. It is present in the largest percentage of cases in the secondary stage, and to a less extent in the tertiary stage and in latent syphilis. The presence of complement-deviating substances in the blood in syphilis points to a sensitisation, and brings syphilis into line with other bacterial sensitisations. **Nakano** did a series of experiments to show that from cultures of spirochætes, or material from syphilitic products by digestion with guinea-pig complement, anaphylatoxin can be obtained.

DESENSITISATION IN SYPHILIS

Comparatively few attempts have been made to desensitise patients with syphilis. As no true immunity is present, it is doubtful whether desensitisation is advisable. If sensitisation results in a series of reactions which are protective in nature, then desensitisation, if it does not lead to immunity, would by removing the protective mechanism lead to a lowered resistance.

Grosgluck used an alcoholic extract of congenital syphilitic

liver and found that, if injected, it acted in all stages of syphilis like mercury, iodides, and salvarsan, but in rapidity and intensity of action it came incomparably after these drugs. The best results were obtained in recurring secondary lesions. Less effect was seen in tertiary syphilis, and still less in recent syphilis. The dose had no visible influence on the success of the treatment in secondary recurring syphilis. In tertiary syphilis as good results were obtained with small as with large doses. No information is given as to the permanency of the results. **Ersettig** treated 14 syphilitics, all with positive Wassermann reactions, with injections of typhoid vaccine. He gave 3 injections, at weekly intervals, of typhoid vaccine. The first contained 500 million typhoid and 250 million para-typhoid bacilli; the second injection double, and the third injection treble that dose; then 2 injections of cholera vaccine containing 2000 and 4000 millions respectively were given. **Ersettig** found these vaccines capable of modifying the Wassermann reaction so as to change it from a strongly positive to a negative reaction. They also caused a modification of the syphilitic lesions, ending in their complete disappearance, even although no antisyphilitic treatment was given.

These results show that non-specific vaccines are capable of modifying the course of an infection like syphilis, but whether, as already stated, the result is in the long run advantageous is very doubtful.

CUTANEOUS TESTS IN SYPHILIS

In 1906 **Jadassohn** made a series of skin tests on syphilitics with an extract of congenital syphilitic liver. He only obtained 1 positive result, and that in a case of malignant syphilis. He thought it was due to an "idiosyncrasy" in malignant syphilis.

In 1908 **Tedeschi** tested syphilitics with a watery extract made from primary sores and obtained weak conjunctival but definite skin reactions. He found the reaction to be absent in healthy individuals and in syphilitics who had been treated with mercury.

In 1909 **Meirowsky,** using an extract of congenital syphilitic liver, obtained positive reactions in 96 per cent. of all syphilitics.

In 116 controls with normal liver extract, in 1 case only he obtained a distinct reaction, and in 2 a slight reaction. He attributed, probably correctly, these control reactions to substances in the liver.

Nicolas, Favre, and **Gauthier** used a glycerine extract of congenital syphilitic liver which they called "Syphilin." They did cutaneous and intracutaneous tests, and obtained much better results by the intracutaneous than by the cutaneous method. **Fontana** used a similar "Syphilin"—a glycerine extract of mucous patches rich in spirochætes. In 51 syphilitics tested in all stages of the disease, 53 per cent. reacted positively, whilst 12·5 per cent. of non-syphilitic cases reacted. This high percentage of reactions in non-syphilitic cases can be explained in the same way as the agar skin reactions obtained by **Stokes** to be referred to later on. The material from the mucous patches might produce the reaction by acting as an adsorbent. **Nakano,** using extract of congenital syphilitic liver—"Pallidin," and **Klausner,** using extract of congenital syphilitic lung, also did similar tests to the previous workers, and obtained high percentages of positive results, especially in tertiary and congenital syphilis.

Up till 1911 the tests were all made with spirochæte-containing material from syphilitic organs, but by the cultivation of the spirochæte **Noguchi** was able to procure from the organism a pure extract which he called "Luetin." Luetin is made by grinding up in a sterile mortar ascitic-agar cultures of the spirochæte and mixing them with a culture of the spirochæte in ascitic fluid. It therefore contains agar diluted with ascitic fluid and the fragmented bodies of spirochætes. As a control, ascitic agar and fluid is used. **Noguchi** first used luetin on infected rabbits, and obtained positive results. Later, he used it on human beings. The test is made intradermically. One-tenth of a c.c. of the luetin is injected into the skin of the left arm, and an equal amount of the control into the skin of the right arm. The injections are given as superficially as possible, separate syringes and needles being used for the luetin and the control. **Noguchi** found that in most cases the control left no lasting trace, whilst the luetin caused different kinds of reactions. In non-syphilitics, as a rule, an erythematous zone developed round the injection spot, and in 24–48 hours a small papule developed,

which began to disappear on the 3rd day. Therefore, only on the 4th day can the result of the injection be read. **Noguchi** obtained 3 types of reaction :—

1. Papular ;
2. Pustular ; and
3. Torpid.

The papular reaction (Plate facing p. 80) occurs especially in secondary syphilis and consists of a red papule surrounded by a diffuse red zone. This reaction disappears in 14 days. The pustular form occurs especially in tertiary and congenital syphilis and in secondary syphilis treated with salvarsan. The original papule develops in a few days into a pustule with a larger zone of redness around it than in the papular reaction. The torpid reaction is the least frequent. It occurs as a small pustule about the 14th day. **Noguchi** found one or other of these reactions to be present in 100 per cent. of tertiary cases with symptoms, in 94 per cent. of latent tertiary cases, in 96 per cent. of congenital syphilitic cases. During the primary and secondary stages of syphilis the reaction is almost always negative except in cases where energetic treatment has been undertaken, especially with salvarsan. In tabes and general paralysis of the insane, **Noguchi** found the reaction positive in about half the cases, and in over 250 control cases he only obtained 1 positive reaction.

Since **Noguchi** first introduced luetin, it has been used by **Gradwohl, Howard Fox, Kammerer, Nobl** and **Fluss, Robinson, Wolfson, Kaliski, Desneux, Marie** and **Broughton-Alcock, Bornstein, Nast** and **Nickau, Tescola, Faginola** and **Fisichella, Perkel, Hanes, Calico, Kolmer** and **Greenbaum** and others. These workers used it in all stages and all forms of syphilis. It is not necessary to give details from all these observers, but on the whole the results were very much the same as those obtained by **Noguchi,** viz. positive results in the great majority of tertiary, latent, congenital, and parasyphilitic lesions and in treated secondary cases, and mostly negative results in primary and untreated secondary cases. The reaction is therefore a very valuable one, because it gives most positive results in the stages of syphilis when the Wassermann is not so frequently positive as it is in the secondary stages.

THE SPECIFICITY OF THE LUETIN REACTION

Neisser and **Bruck** found that a reaction similar to that produced by syphilitic liver extract could be obtained also with a concentrated extract of normal liver. Therefore the reaction is not specific. **Neisser** ascribes it to the condition of "Umstimmung" in the late stages of syphilis, but, as already stated, non-specific agar reactions can be produced and the reaction is probably not an antigen-antibody reaction but an antiferment-adsorbent reaction. **Boas** and **Ditlevsen** obtained positive reactions in tertiary syphilis, using gonococcal and colon bacillus suspensions. Working with luetin they also obtained positive reactions in cases where there were no signs of syphilis. Also the control fluid frequently gave positive reactions, probably from the agar which it contained. Therefore there is an altered sensitiveness of the skin in tertiary syphilis, but what the exact explanation is, has not yet been fully explained. **Boas** and **Stürüp** also obtained positive reactions in late syphilis, using extracts of enlarged glands from cases of soft sore. **Chieffi** likewise found the luetin reaction to be positive in other conditions besides tertiary syphilis. Lupus, leprosy, trichophytosis, simple folliculites, and ecthyma reacted positively. He also confirmed **Boas** and **Ditlevsen's** results with gonococcal vaccine instead of luetin.

Lagano and **Broughton-Alcock, Nobl** and **Fluss, Schmitter, Burnier,** and **Kolmer** and **Greenbaum** also obtained non-specific reactions with luetin. **Stokes,** as already mentioned, produced positive reactions by intradermal injection of solutions of agar in physiological serum. He found the reaction positive in 50–70 per cent. of the cases of tertiary syphilis. **Kolmer** and **Broadwell** found that there was no direct relationship between the presence of the luetin reaction and the presence of agglutinins and complement-fixing bodies in the serum. Therefore they conclude that the test cannot be regarded as an index of the resistance to the spirochæta pallida. **Bornstein, Nast,** and **Nickau** also found that a non-specific lytic action is developed in the blood after luetin injections.

In 1915 **Sherrick** found that a 0·5 per cent. suspension of agar, if injected intradermically, gave rise to reactions indistinguishable

from the luetin reaction, provided that the patient was taking potassium iodide. He also found that normal persons taking potassium iodide gave positive luetin reactions, and that the luetin reaction in syphilitics, when involuting, could be revived by the same drug. **Kolmer, Broadwell,** and **Matsunami** confirmed **Sherrick's** work, obtaining well-marked positive luetin reactions in healthy persons taking potassium iodide. **Borbeg** and **Cole** and **Paryzek** also found the same reactions in persons taking iodides. **Kolmer, Immerman, Matsunami,** and **Montgomery** found that, in addition to iodides, bromide of potassium and sodium, when taken internally, caused similar but less marked reactions to luetin. The chlorides of potassium and ammonium only influenced the luetin reaction to a very slight extent. The administration of protiodide of mercury also influenced the luetin reaction to some extent. Ether and chloroform anæsthesia did not seem to influence skin reactions. Cutaneous tests were not as readily influenced by iodides as intracutaneous tests. These observers also found that the administration of potassium iodide, and, to a less extent, of potassium bromide, increased the phagocytic power of the blood serum for bac. prodigiosus. They think that the increased severity of skin reactions in persons taking these drugs may be due to heightened leucocytic infiltration and phagocytosis at the seat of injection or to an increase of tryptic activity through the saturation of fatty-acid radicals according to the hypothesis of **Jobling** and **Petersen**. **Stokes**, in doing his agar reactions in normal individuals, found that iodides, taken internally, appeared to favour a reaction, just as they do in the luetin test.

Therefore, before doing the luetin test, the physician must always be careful to ascertain that the patient is not, or has not recently, been taking iodides or bromides.

SUMMARY

1. The rashes in the secondary and tertiary stages of syphilis can be explained on the principles of sensitisation to the spirochæta pallida.

2. An active immunity to syphilis has never been produced.

3. Experiments to produce passive immunity to syphilis were also unsuccessful.

4. There is no true immunity to syphilis. Persons with syphilis are protected from reinfection by the local hypersensitive reaction which occurs at the seat of reinoculation.

5. Malignant syphilis is probably due to a very high degree of sensitisation of the individual and not to an increased virulence of the spirochæte.

6. The Wassermann reaction, although not a specific antigen-antibody reaction, is sufficiently constant to be of use clinically, especially in the secondary stage.

7. The intracutaneous reaction to luetin, although not specific, is useful clinically, especially in tertiary, latent, and congenital syphilis. The administration of iodides or bromides vitiates the test.

8. Desensitisation to syphilis with organ extracts and non-specific vaccines has been attended with partial success, but further work is required before a definite opinion can be expressed as to its value.

CHAPTER IX

SENSITISATION AND IMMUNITY TO FUNGUS INFECTIONS

Ringworm and favus have been looked upon, until comparatively recently, as purely local infections. The well-known clinical appearances of the skin lesions were recognised and described by all the older writers. That they were due to the presence of a fungus in the skin was also known. Whilst the skin is the usual seat of the lesions, in rare cases (such as those recorded by **Robertson** and **Cutler** and **Gilletti**) ringworm has been reported as affecting the mucous membranes of the mouth. There is also the well-known case of favus described by **Kaposi** with lesions in the gastro-intestinal tract.

In all these cases the infection was considered as a purely local one affecting the skin and mucous membranes only. The one isolated fact which suggested some general effect, was that it has been known for some time that farm workers and others who have suffered from an attack of cattle ringworm on the body and limbs are immune to further attacks. In these cases the lesions were usually extensive, deep seated, and accompanied by suppuration.

A great deal of work was done, especially by **Sabouraud,** on the investigation into and cultivation of the different fungi which cause ringworm and favus in man and animals, but that work did not advance our knowledge as regards the changes which take place in the body during or after an infection with these diseases.

In 1887 **Cohen** showed that the course of an infection with aspergillus flavescens was influenced favourably by a previous infection with the same fungus, but the first work bearing directly on this question was published in 1902 when **Neisser** reported the results of some experiments done by himself and **Plato** on

human beings suffering from ringworm and favus. These workers made an extract of the ringworm fungus which they called "Trichophytin." The fungus was grown at room temperature in flasks containing 1 per cent. Witte's peptone, 3 per cent. maltose, and 0·5 per cent. NaCl for 3 months. The mass of fungus was cut into pieces and bruised down so as to separate the elements as much as possible. The whole was then filtered through sterile filter paper, the filtrate tested for sterility, and 0·25 per cent. carbolic acid added as a preservative. This trichophytin therefore corresponded to the old tuberculin prepared from the tubercle bacillus.

It was found that, when this trichophytin was injected into a patient suffering from a deep-seated ringworm, it produced a general reaction with rise of temperature and symptoms of intoxication. It also caused a local reaction at the seat of injection, which became hyperæmic and sometimes suppurated. In these experiments no therapeutic effect on the lesions was noticed.

The trichophytin produced no local or general reaction in healthy men nor in those suffering from other diseases such as tuberculosis. As a control, some of the culture medium was injected, but had no effect on the ringworm patients.

It was found that a reaction only occurred in patients suffering from deep-seated ringworm, the reaction being entirely absent in superficial tineas.

"Favin," an extract of favus fungus, prepared similarly to the trichophytin, gave no reaction ir favus cases, and favus cases gave no reaction to trichophytin.

These experiments showed that in deep-seated ringworm, but not in superficial cases, some change had taken place in the patient's tissues which resulted in a general and local reaction. In other words, the patient had become sensitised to the infecting agent.

As a result of this work by **Neisser** and **Plato** many other workers started experimental investigations in ringworm in man and animals.

Bloch working alone, and also with **Massini**, did a great many experiments on man and animals. **Bloch** was the first to prove experimentally that immunity resulted in animals after an

infection with ringworm. He found that certain kinds of trichophyton fungi are pathogenic for guinea-pigs and rabbits. These animals, if properly inoculated, developed the disease with certainty every time. He found that Achorion Quinckeanum (the fungus of mouse favus) and Trichophyton gypseum were the fungi which most readily infected animals. When an animal is inoculated with either of these fungi a typical local lesion develops, but spontaneous involution takes place beginning usually in 7–9 days after inoculation. All animals after a single infection (except when the primary spot is a very small one) are immune to further infection. This immunity was found to last in animals at least as long as a year and a half, and coincident with the immune reaction it was found that the skin had become sensitised, as was shown by the presence of a cutireaction, which will be referred to again later.

Specificity.—Two interesting facts also emerged from these experiments. Firstly, it was found that this sensitisation and immunity were not strongly specific. The reaction is only specific for trichophytosis in general. An animal which had passed through an infection with Achorion Quinckeanum, and in which immunity had been produced, could no longer be re-infected with that fungus, but the same animal was also found to be immune to infection with Trichophyton gypseum. This shows that the achorions (favuses) and the trichophytons are very closely allied, and **Bloch** even goes so far as to claim that Achorion Quinckeanum is really a trichophyton which forms scutula.

Secondly, it was found that the only way to produce complete immunity was by skin inoculation, and that the lesion must be a deep one. Intraperitoneal and subcutaneous inoculation did not produce the same results. **Bloch** thinks that this is because the conditions necessary for the oxygenation of the fungus are so unfavourable inside the body that its growth and the production of immunising substances are interfered with.

Bloch and **Massini** also found that the size of the focus is of no importance for the occurrence of immunity. Likewise immunity is only obtained by inoculating with living cultures and producing an actual infection. Trichophytin and favin, if injected previously, were found not to confer immunity and did

not make the animal hypersensitive. This corresponds to what is known to occur in tuberculosis, where injections of tuberculin do not cause the skin to become allergic, whereas an actual infection with tuberculosis always leads to the production of a positive tuberculin skin reaction. Similarly, **Axamit** in 1907 showed that injection of dead fungus from blastomycetes is not capable of producing hypersensitiveness, but living fungus can do so.

Following **Bloch** many others did experiments on similar lines.

Bruhns inoculated several varieties of trichophyton cultures into animals and human beings. The stronger cultures such as **Bloch** used (Trichophyton gypseum and Achorion Quinckeanum) were found to cause an immunity. Cultures of other kinds did not do so. Those which caused the deep forms of tinea left more immunity behind them than those causing the superficial forms, but individuals were found to vary. **Bruhns** thinks that in most cases absolute immunity is not obtained. The immunity is only relative. An attempt to cure a case of tinea in men by repeated inoculation was not successful.

Bruhns and **Alexander** did a great many experiments by inoculating guinea-pigs with trichophytons, microsporons, and favus. When using the same fungus as **Bloch** had used they obtained the same results as he did, thus confirming his work. On the whole, they found that an infection with ringworm in guinea-pigs and man produces only a relative but fairly marked immunity. They also confirmed, what has been long known with regard to deep-seated kerion ringworm, that fungi which produce deep-seated lesions have a greater immunising power than those which produce superficial ones. One may get a tinea barbæ with deep, lumpy lesions or superficial rings due to the same fungus. Therefore the difference is not due to the fungus itself. In the former case immunity results. In the latter it is absent. It all depends on whether the fungus comes into contact with the tissues of the body and produces a cellular reaction there.

Citron also repeated **Neisser** and **Plato's** experiments by injecting trichophytin, but did not succeed in getting any positive reaction even in deep-seated ringworm cases. This, however,

may have been due to his cultures being old and having been repeatedly subcultured, whereas **Plato** worked with cultures direct from man.

Hanawa did experiments by inoculating animals with Trichophyton gypseum as **Bloch** did, and found that in guinea-pigs the lighter-haired areas became more quickly immune than the darker-haired areas. He also excised the skin lesions in normal and immune guinea-pigs to see what change takes place as immunity develops and the lesion heals. He found that, corresponding with the clinically rather sudden tendency to healing after 7–9 days, the relatively subacute inflammation which arises on first inoculation passes on to a very acute necrobiotic inflammation.

The necrosis leads to sloughing of the surface layers and the formation of a crust in which well-stained fungus elements are thrown off. The healing takes place in the first instance, not by destruction of the fungus, but by its elimination in the crust.

Kusonoki also did a great many inoculation experiments on animals, and found that in guinea-pigs an immunity can be produced by all kinds of fungi, so that the animal can neither be reinfected locally nor in any other part of the body surface, either with the same fungus or one of the same group. A very virulent fungus produces an immunity against slightly virulent fungi, but the immunity produced by a slightly virulent fungus is not strong enough to prevent infection with a very virulent fungus. Like other workers, **Kusonoki** also found that the deeper the focus of disease, the more quickly and strongly the immunity developed. Not only the quantity but also the quality of the fungus endo-toxin is of great importance in producing immunity. It was found that it was more difficult to produce immunity in rabbits than in guinea-pigs, and that there is a certain relation between immunity and body weight. The immunity in animals can be inherited either in the case where the mother's immunity is acquired before conception or during the pregnancy. **Kusonoki** found that the immunity produced is a relative one only, and that in some cases on second inoculation an abortive infection took place. Numerous experimental observations in ringworm were also made by **Prytek.** This observer, like **Kusonoki** and others, found that infection of guinea-pigs with ringworm of

the skin always led to a state of sensitisation which showed itself by the fact that repeated inoculation either led to no result or to a modified form of the disease. This modified form of the disease came on quickly and ran a rapid course, and is to be looked upon as a hypersensitive reaction rather than a true reinfection. **Prytek's** experiments yielded varying results. On the one hand, complete immunity did not always result from infection with a fungus which produced deep foci, and, on the other hand, fungus from superficial lesions sometimes immunised completely. One experiment was done on man, and did not lead to an immunity. The person experimented upon was a doctor who allowed himself to be inoculated on the arm with Achorion Quinckeanum. A typical red scaly lesion was produced in which the fungus was found. The lesion suppurated and was cured by the application of Tinct. Iodi. Nine months later the same arm was inoculated with Trichophyton gypseum, and a scaly, ringed lesion with blisters at the edge developed and ran a course of some weeks. The same experiment done by **Bloch** previously had produced a complete immunity to reinfection, but in this case no real immunity had been produced.

Truffi also did a great many experiments on men and animals. By subcutaneous injection of trichophytin he obtained local and general reactions, and usually focal reactions as well in deep ringworms. In superficial cases of ringworm he succeeded in producing a fairly good reaction by the application of croton oil to the lesions, thus causing a deep-seated action of the fungus. Reactions occurred irrespective of whether the causal fungus of the ringworm was the same as the one used to manufacture the trichophytin. Reactions were also obtained with "microsporin," but to a less degree than with trichophytin. No reactions were obtained with trichophytin in cases of favus.

Lombardo came to the conclusion from a series of experiments that inoculations with fungi are only able to bring the body into a state of allergy, which is shown by an altered and more rapid course of the disease. He did not succeed in producing a real immunity. On reinoculation what was produced was not to be considered as a modified reinfection so much as an allergic reaction due to the presence of the fungus and its toxins.

Lombardo also quotes **Skrinski,** who used Achorion Quinckeanum, Microsporon lanosum, and Trichophyton asteroides as always obtaining an immunity after one attack of the disease.

Lombardo found that the allergy produced by an attack of the disease persisted as long as a year and a half after the disease had healed. It is not strongly specific for the fungus which first caused it. He could not produce allergy either by injection of living or dead hyphomycetes under the skin or by intramuscular or intravenous injection of toxin or culture filtrates. As others found, it required an actual attack of the disease to cause sensitisation and immunity.

Prytek's animal experiments were very thorough, as many as 359 inoculations being made on 227 animals (guinea-pigs and rabbits). As stated, his results varied from an absolute immunity to very little immunity at all, but he never saw a single case where the second infection ran the same course as the first. Therefore the first infection always had some sensitising or immunising effect. This sensitisation or immunity is not a local one, but a general one affecting the whole skin.

Saeves also repeated the experiments of **Bloch, Kusonoki, Bruhns** and **Alexander**, and **Prytek,** by inoculating animals with Achorion Quinckeanum and Trichophyton gypseum because the fungi have been shown to be very constant in their ability to produce ringworm in animals. **Saeves** found that during the clinical incubation time of guinea-pig ringworm it was possible to demonstrate fungus, both culturally and microscopically, more or less abundantly in the skin. The inflammatory signs are slight, and remain so till the development of hypersensitiveness, when the typical clinical lesion appears. This agrees with **Pirquet's** work on Vaccinia, and shows that in the dermatomycoses the incubation period lasts till the moment when the specific hypersensitive reaction reaches its height, and then the healing process begins, by an elimination of the fungus. **Saeves,** too, like **Prytek**, found that on reinoculation of animals a modification of the course of the reaction always occurred. True complete immunity in the clinical sense was only found exceptionally ; complete immunity was developed especially after repeated inoculation. Most often the reaction appeared sooner and ran a shorter course than after the first injection, and it appeared sooner after a shorter

incubation period, but on the whole the general characters of the modified lesion were very like the typical acute disease. Very often from the reinoculated areas abundant fungus was found microscopically, so that there was no doubt that it was multiplying in the skin. **Saeves** also found that after the reinoculation has run its course there occur peripheral nodules (containing fungus) arranged in a corymbiform manner similar to the trichophytides in human beings to be described later on.

Saeves also investigated why some types of ringworm, such as Achorion Quinckeanum and Trichophyton gypseum, will produce a typical clinical lesion in animals on almost every attempt, whilst Epidermophyton inguinale and Microsporon Audouini do not. He found that he could cultivate the latter fungi from the skins of inoculated animals 10–15 days after inoculation, showing that a rapid death of the fungus, when applied to the skin, is not the cause of their non-pathogenicity. This disposes of **Bloch's** view that the guinea-pig has an inborn natural resistance to Microsporon Audouini, and, therefore, the fungus dies rapidly on the skin. The most likely explanation is that Microsporon Audouini and similar fungi fail to bring the skin into a state of sensitisation, and, therefore, into the possibility of reaction, and thus no clinical lesion results.

These experiments of **Saeves** are important from a practical point of view. They show that fungus may lie and grow on the skin without producing a clinical lesion, and if that occurs in animals it might also occur in human beings, who might transmit the disease without themselves suffering from it. A mother might act as a carrier and carry infection from one child to another without herself showing any visible skin lesion.

Saeves also, by intracardial injection of guinea-pigs with a spore-suspension of Achorion Quinckeanum and Trichophyton gypseum, succeeded in producing more or less widely distributed hæmatogenous trichophytic skin lesions which corresponded in their clinical and histological picture with those produced by skin inoculation. Similar intracardial inoculation of Achorion Schönleinii and Epidermophyton inguinale produced no lesions. If lesions are produced by the hæmatogenous route, allergic signs are produced. In all experiments hitherto done by others in animals allergic to ringworm, intracardial injection produced

very varying results; either rapidly healing nodules containing fungus or more or less atypical ringworm foci.

Thardshimanjanz likewise studied immunity reactions in guinea-pigs with ringworm, and came to the conclusion that animals which have once had tinea give a positive reaction to injection of trichophytin.

Tomasczewski, working with Achorion Quinckeanum on guinea-pigs, rabbits, cats, dogs, and hens, found that guinea-pigs developed lesions with scutula, which rapidly fell off with intense local inflammatory signs. One such attack left a lasting immunity behind. Whereas with rabbits, cats, dogs, and hens more frequently he got a more or less long-standing favus with much less inflammatory reaction. Therefore he concludes that the duration of the lesion depends on the intensity of the reaction.

Lombardo's experiments on animals with many kinds of ringworm fungi on the whole confirm the results obtained by others. He obtained after a positive inoculation a condition of allergy which was manifested by symptoms of reaction and an atypical short-lived lesion on later inoculation. He never produced a true immunity by inoculation. The allergy persisted long after the lesion had healed (even after 18 months), but gradually tended to diminish. It was found not to be strongly specific for the fungus which first produced it. It is not transmissible from mother to young, and showed itself most distinctly in grown animals after puberty, and castration did not modify it. No allergy could be produced either by injection of living or dead fungus under the skin or by intramuscular or intravenous injection of toxins or culture filtrates.

Sabouraud inoculated guinea-pigs with different ringworm fungi and found that it was impossible to use the same animal twice, as the first attack had sensitised the animal. From his researches he came to the conclusion that the greater the inflammatory reaction produced by a given trichophyton in man the greater the immunity it confers when inoculated in the guinea-pig, and probably also in man.

Analogous experiments to those with ringworm fungus were done by **Ribbert,** who worked with aspergillus. He showed that rabbits which had been previously injected intravenously with

aspergillus spores showed a milder reaction when the aspergillus spores were injected into the anterior chamber of the eye than occurred in rabbits not previously injected. The reaction in the eye appeared sooner than in the animals not previously injected, and was manifested by the lesser number of leucocytes in the inflammatory reaction.

Martenstein demonstrated that the skin epithelial cells as well as the blood serum of a guinea-pig infected with Achorion Quinckeanum contains certain specific "bodies," which, if brought into contact with the living spores of Achorion Quinckeanum in vitro, produce a toxic substance. This toxic substance, if injected intradermally into a normal animal, produced a local inflammatory infiltration at the seat of inoculation. This toxic substance was found to be thermolabile, whilst the specific bodies are thermostable. A later investigation by the same author showed that in a guinea-pig infected with Achorion Quinckeanum for the first time the specific bodies appear at the injected area after 6 days, in the blood serum after 7 days, and in the unaffected epidermis after 8–9 days. If the injection area is excised in toto (within 1–4 days) the specific bodies appear first in the unaffected epidermis after 8 days, and then later in the blood serum. The duration of the reaction produced in a guinea-pig which has been injected intradermally with the toxic substance corresponds to the length of time during which the animal has been infected with Achorion Quinckeanum. The oftener the toxic substance is injected, the shorter the duration of the reaction. In animals which have gone through an infection with Achorion Quinckeanum the reaction is very slight. By repeated intradermal injection of this toxic substance it is possible to produce an ever-increasing immunity in a normal guinea-pig, and repeated subcutaneous injection of the toxic substance leads to a reaction in the subcutaneous tissues which runs a chronic course.

This work of **Martenstein's**, therefore, seems to show that Achorion Quinckeanum produces a specific antibody first at the seat of injection, and this antibody is carried by the blood serum to the cells of the rest of the skin. Whenever fungus elements are introduced and come into contact with the specific antibody, a toxic substance is produced which leads to an inflammatory reaction. This would account for the local and focal trichophytin

reactions, for the cutaneous trichophytin reaction, and for the trichophytides.

I have given the foregoing rather detailed account of inoculation experiments with ringworm and favus, because I feel that, except to those who have worked at the subject, they are very little known. From a survey of them all, it may be safely concluded that in animals at least, and probably also in man, infection with ringworm always leads to a more or less marked sensitisation. Whether this is associated with a real immunity is more difficult to determine, but all the evidence goes to show that given a deep-seated ringworm lesion, it leads to an immunity. The lesion often produced on reinoculation is not a true reinfection. It is to be looked upon as a hypersensitive reaction, and when **Prytek** and others speak of a relative immunity because they obtained a modified lesion on reinoculation, the whole question of the relation of sensitisation to immunity is raised. This question will be discussed later under the cutaneous tests which occur not only on a sensitised skin, but in an immunised one as well.

LOCAL IMMUNITY OF THE SKIN TO RINGWORM

As already mentioned, all the workers who inoculated animals with ringworm found that after an animal had passed through an attack of the disease, its skin on reinoculation either showed a complete immunity or reacted in a different manner from the first occasion. This was found in all cases not to be a local immunity or altered reaction, but a general one affecting the whole skin.

I have only been able to find 3 references to local immunity in ringworm. The one was a discussion on this subject in 1910 by **Blaschko,** who brought forward the theory that ringworm spreads in circles and heals in the centre because a local immunity occurs in the infected centre. He quotes a case of extensive tinea on the chest and back which spread always outwards and never recurred on the previously infected areas. He suggests that there may be a local immunity produced in the skin cells where the parasite has been. Against this theory is the fact that one may get cases where there are numerous concentric

rings, the fungus still being active in the central rings, whilst it still spreads at the peripheral ones. It is not often that one sees 2 ringworm lesions so close together that they run into one another, but I have no recollection of ever having seen 2 completely ringed lesions overlapping one another. The more usual result is for the patches to fuse and form a single larger one with a circinate outline.

Citron, doing experiments on mice with mouse favus, which heals with scar formation, found that if one injects into this scar, after complete healing, a not too large amount of favus emulsion, the infection either does not take place or is very slight. He thinks this is probably not a local immunity, but is due to anatomical changes in the scarred skin. **Kusonoki** quotes **Menschen** as having found after trichophytosis that there remains a local immunity, but he does not give the source of his information. **Jadassohn** suggested that in superficial tineas which had healed in the centre, the central area should react more strongly to trichophytin than normal skin, if the central one heals as a result of sensitisation there ; but he found this not to be the case. As recurrence often occurs in such central healed areas, he thinks that the healing in the centre is due to the nutritive material being used up in the central area rather than to any local immunity. If recurrences do occur in a central healed area they do not cause any specially intense inflammatory reaction such as one would expect if that area were hypersensitive. The fact that the disease may recur in a previously affected area is against any local immunity being present.

ACTIVE IMMUNITY IN RINGWORM AND FAVUS

Several observers have attempted to produce an active immunity in animals. **Bloch** and **Massini** injected animals with the juice of the fungus and culture filtrates previous to infection, but found it did not prevent infection taking place.

Citron also found that in guinea-pigs, injection with dead cultures or filtrates before inoculation, or simultaneous injection at the same time as inoculation, had as a rule no effect on the development of the lesion, but in 1 case the lesion seemed to heal more quickly than usual. He also did a series of experiments

on white mice with mouse favus (*Achorion Quinckeanum*), human favus, and microsporon. He found that previous injection of dead culture emulsions caused a certain increase of resistance in susceptible animals when inoculated later with emulsions of living cultures. These above experiments were done by intraperitoneal injection of both dead and living cultures. He also did another series of experiments to see whether immunity could be produced by subcutaneous injections, and obtained similar results.

Therefore he concludes that an active immunisation is to a certain degree possible in ringworm and favus as in tuberculosis.

Kusonoki, in spite of different modifications of technique, never succeeded in producing active immunisation with trichophytin or dead fungus extracts, but in a few cases a mild or abortive form of the disease was to be seen in immunised animals.

Pecori also failed to produce an active immunity by injection of trichophytin.

But **Bloch** succeeded in partially immunising guinea-pigs by repeated prolonged rubbing of the skin with fungus killed by heat. He therefore concludes that immunity in guinea-pigs to trichophytosis can be produced through the skin, and it was found to be immaterial whether living or dead fungus is used.

Sutter similarly found that prolonged rubbing of sterilised fungus into the skin of normal guinea-pigs leads to a partial immunity, but the same result can be obtained by repeated intradermal injection of a concentrated trichophytin. The result produced is the same as in an animal which has become partially immune after a slight ringworm infection.

PASSIVE IMMUNITY TO RINGWORM AND FAVUS

As in active immunity several observers have done work in an attempt to produce passive immunity, **Bloch** and **Massini** were unsuccessful in producing passive immunity with serum and skin extracts of immune animals.

Citron tried to get a serum against fungus infections. He began with intraperitoneal injections into rabbits of dead culture emulsions, and then later gave intraperitoneal injections of living cultures, and, from time to time towards the end of the immunising

process, intravenous injections of culture filtrates. The animals stood intraperitoneal injections well, but some died after the intravenous injections. Some of the animals were treated thus for 8 months. The serum in numerous experiments on mice showed neither a protective nor a heating effect.

CHANGES IN THE BLOOD IN RINGWORM AND FAVUS

Miescher, in 1915, found that in the deep forms of ringworm, as was to be expected, there is a more or less marked leucocytosis. The leucocytosis is a polymorphonuclear leucocytosis with an absolute diminution of lymphocytes. The superficial forms of ringworm show no such change in the blood picture. Injection of trichophytin, either intradermically or subcutaneously, in ringworm cases also produced the characteristic polymorphonuclear leucocytosis. This occurred markedly in deep-seated ringworm cases and with trichophytin made from a fungus which produces a deep lesion. In superficial tineas it is less constant, but, if present, is the same as in deep cases. Persons who had not had ringworm previously may react to trichophytin injection with a leucocytosis, but in this case it is always due to an increase of lymphocytes. **Bloch** had previously shown that, if trichophytin be injected subcutaneously into a patient with ringworm, general symptoms of illness, swelling of glands, local and focal reaction occur, and also a leucocytosis in the blood.

The blood changes described by **Miescher** and **Bloch** in ringworm and after trichophytin injections were confirmed and extended by **Sutter** (*Weitere Beiträge*). He found that in healthy individuals during the incubation stage an injection of trichophytin produces a slight lymphocytosis. In ringworm cases and immune persons it produces a polymorphonuclear leucocytosis which gradually diminishes on repeated injections. In cases of ringworm when there is an already existing polymorphonuclear leucocytosis, each intradermal injection of trichophytin caused a further increase of polymorphonuclear leucocytes in the blood.

In 1916 **Strickler** examined the blood in 60 cases of tinea capitis and 4 of favus. He found that in tinea capitis there is

an increase of the small lymphocytes in the blood. The average differential count showed 37·4 per cent. of lymphocytes. This lymphocytosis was present in 80 per cent. of the cases. In the 4 cases of favus a small increase of lymphocytes was also found. **Strickler** considers that this lymphocytosis is sufficiently constant to be of value in the differential diagnosis of tinea capitis.

SERUM CHANGES IN RINGWORM AND FAVUS

As the deep-seated ringworms produce an immunity, one would expect that it would be possible to demonstrate the presence of antibodies in the blood serum of such cases. The fact that in animal experiments the injection of trichophytin causes local, focal, and general reactions also points in the same direction.

Citron examined the serum of animals for the presence of agglutinins and precipitins. He found it impossible to do agglutination tests because the fungus was in masses and could not be separated easily. But he infers that agglutinins are present because when the fungus is injected intraperitoneally, as a rule it is found massed together in clumps and not floating loose in the peritoneal fluid. He found the presence of precipitin in the serum. The reaction did not occur if the serum was very diluted, and normal serum caused no precipitation. It was also found that the reaction was not specific. The serum of an immunised animal gave a positive precipitation test with all ringworm and favus fungi, but the one with which the animal was immunised showed itself more sensitive than the others. This fact also supports the conclusion already come to as a result of inoculation of animals that the different varieties of ringworm and favus fungi are very closely related biologically.

Sutter found that in isolated cases of deep-seated human tinea at the height of the disease the serum contains complement fixing substances and precipitins. In his investigations he used trichophytin as antigen. In the majority of cases in man, however, and in all cases in animals, the results were negative.

He also exposed trichophytin to the blood serum of ringworm patients and healthy individuals for some hours. This trichophytin was used for intradermal skin tests in ringworm and normal individuals and the results found to be the same as those produced

by ordinary trichophytin. Therefore he concludes that the presence of antibodies in the serum of ringworm cases has not been demonstrated. He further tried to see if he could get any better results in " vivo." He froze an area of skin with CO_2 snow in normal and ringworm cases. The serum was then drawn off from the blisters produced by the freezing, and trichophytin was injected into the blister and again withdrawn some hours later. This was used to do skin tests, but the results were exactly the same as when ordinary trichophytin was used. Similarly, negative results were obtained by using the fluid obtained by puncture of lymphatic glands of healthy and ringworm cases, mixing this with trichophytin, and doing skin tests with it. The results were all negative.

He also did experiments, similar to those done by **Dale** and others, on the intestine of animals. A guinea-pig, immune to ringworm, was killed and the intestine suspended in Ringer's solution. Even although 3 c.c. of trichophytin were added to the Ringer's solution, no contraction of the bowel occurred. **Sutter** therefore failed to find in the blood or serum of ringworm cases or in ringworm hypersensitive animals or man (apart from a fairly strong complement fixation in the serum of a few highly allergic ringworm cases) the presence of specific antibodies. He therefore concludes that ringworm hypersensitiveness is not a true anaphylaxis, and quotes in support of this the fact that immunity or allergy to ringworm have not been passively transmitted ; nor can active immunity be produced by trichophytin injections. Whereas **Bloch** only succeeded in producing a partial immunity by repeated prolonged rubbing of dead or living fungus into the skin. It would seem, therefore, that the hypersensitive or immune condition produced in ringworm is due not to a serum reaction, but to some local change in the skin cell itself. This will be referred to again later when **Bloch's** transplantation experiment is discussed.

Pecori, like **Sutter,** obtained weak but definitely positive complement fixation and precipitation reactions in some cases of human tinea, using trichophytin as antigen.

Caroll tested the serum of 18 cases of ringworm, and found that in marked cases of deep-seated ringworm it was possible to get a positive complement fixation reaction with a trichophytin

antigen. In superficial forms of ringworm, which had existed for some time, a partial fixation may occur. In favus capitis and corporis the reaction was always negative. The serum should, if possible, be examined within 24 hours after withdrawal and should be used undiluted or half-diluted. Serum from normal individuals and individuals suffering from other diseases always gave negative results.

Using a mass of emulsified fungus, **Kusonoki** found that complement fixation and precipitation tests with sera of men and animals with ringworm gave only uncertain results.

Saeves tried to prove the presence of ferments from the ringworm fungus in the serum of men allergic to ringworm. He used the Abderhalden test, but failed to find any evidence of the presence of defensive ferments. **Costa** and **Fayet** did agglutination and complement fixation tests with the serum of horses which had suffered from ringworm, but the results were all negative. This was to be expected as the disease in these cases was a superficial one, and was shown by successful reinoculation not to have produced any immunity.

Kolmer and **Strickler** examined the sera of 27 cases of tinea capitis due to Microsporon Audouini, 3 of favus capitis due to Achorion Schönleinii, and 1 of pityriasis versicolor. He found that, with a polyvalent antigen of Microsporon Audouini, complement fixation was found to occur in 78 per cent. of patients suffering from tinea capitis. This is rather surprising in view of the fact that small-spored tinea capitis is a superficial invasion of the hair follicle only. **Kolmer** and **Strickler** think that it is conceivable that the fungus produces soluble products which are capable of absorption and of stimulating the local and general body cells to produce antibodies.

The sera of 2 cases of favus out of 3 gave positive complement fixation reactions, using Achorion Schönleinii as antigen. This is not to be wondered at, as favus is a much deeper infection than small-spored tinea capitis, the fungus actually growing in the skin itself.

The degree of reaction to both ringworm and favus was found to depend on the severity and duration of the infection. The ringworm and favus antibodies (amboceptors) fixed complement best with their respective antigens, but with relatively

large doses of serum this specificity was not observed. Here again a biological relationship between the ringworms, even small spored, and favus was demonstrated.

A culture from the scales of the case of pityriasis versicolor, which **Kolmer** and **Strickler** regarded as a doubtful culture of Microsporon furfur, reacted weakly or irregularly with the sera of ringworm and favus patients, and negatively with the serum of a case of pityriasis versicolor.

In all these tests the authors used the sera of syphilitics and that of persons suffering from scabies, impetigo contagiosa, eczema, acne vulgaris, and other diseases as controls, but in no case did the sera give any complement fixations with the antigens of the fungi.

Like **Citron** and others, **Verrotti** found a want of specificity in the complement fixation test. He obtained a culture of Microsporon lanosum from a case of ringworm of the scalp. A dog was infected with this fungus. The dog's serum gave a positive reaction with several fungus antigens, and curiously enough a more marked reaction with Trichophyton gypseum, Tr. rosaceum, and Tr. accuminatum as antigen than with Microsporon lanosum. Complement fixation tests were also done by **Blumenthal** and **Haupt.** They examined the sera of patients with deep-seated ringworm, and in the majority of cases found the presence of complement fixing antibodies. They used the ordinary technique the same as in the Wassermann test, but with fungus antigens which they prepared themselves. In superficial tineas antibodies were found only exceptionally. Usually the quantity of antibody was proportional to the severity of the disease. An interesting point was that allergy reactions and antibody formation did not always run parallel. Cases previously treated with trichophytin all showed complement fixation. It was also found that the complement fixation reaction was just as little specific as the allergy reactions. It occurred also in sycosis and in gland tuberculosis. From their results **Blumenthal** and **Haupt** conclude that one cannot speak of the immunity which occurs in deep-seated ringworm as a cell immunity. Humoral immunity changes play a part in the defensive mechanism.

Schreus and **Goehl** obtained similar positive complement

fixation reactions in deep and superficial ringworm cases. "Trichon" (**Höchst**) was used as antigen, but no details are given and only a few cases were tested. That the serum change was not due to any reaction or absorption from the X-rays used in the treatment was shown by the fact that positive reactions were usually obtained before the cases were X-rayed as well as afterwards.

Nathan also came to the same conclusion. He obtained non-specific complement fixation reactions in 3 deep ringworm cases, using the different preparations of trichophytin, and in 5 cases (superficial ringworm, gonorrhœa, and syphilis at various stages) the reaction was negative. These negative results in the controls, however, were only obtained when a special trichophytin prepared by **Höchst** was employed as antigen. Precipitation tests were also made, using the special preparation of **Höchst** trichophytin, and in 12 sera from trichophytosis profunda, 7 were positive, 2 doubtful, and 3 negative. Two sera from superficial ringworm were negative. Here also the precipitation tests were non-specific, as the sera of 4 syphilis patients gave a positive reaction. Different samples of trichophytin gave different results.

Therefore **Nathan's** results, together with those of **Bloch, Pecori, Sutter, Caroll,** and **Blumenthal** and **Haupt,** show that at least in deep-seated tineas in men the immunity processes are not dependent exclusively on the formation of a skin allergy and immunity, but that antibody formation in the blood serum plays a part.

The general symptoms such as fever, swelling of glands and spleen, and the leucocytosis in the blood in deep tinea cases, also point to the probability of fungus elements circulating in the blood and coming into contact with antibodies in the blood, thus leading to the production of toxic substances which cause the general symptoms. **Kusonoki, Saeves,** and **Sutter** all noticed general symptoms in guinea-pigs which had been repeatedly inoculated with tinea. They went out of condition and often died. **Sutter,** too, noticed that some of his animals died a day or two after reinoculation with ringworm, and post-mortem no gross pathological lesions were to be found. **Sutter** thinks these were probably chronic anaphylactic deaths.

He also quotes the fact that trichophytides occur as a point in favour of the presence of antibodies in the blood just as the rashes in the specific fevers are probably due to the same cause, and thinks that the circulation carries the antibodies and gives them up to the skin tissues and saturates them so that if fungus elements again circulate, a reaction takes place between this circulating fungus and the allergic skin with the production of the trichophytide. The fact, too, that man and animals after an attack of deep-seated ringworm show an allergy of the whole skin means that the substances necessary to produce this allergy must have been carried there by the circulation. This subject will be referred to again later under Trichophytides.

CUTANEOUS REACTIONS IN RINGWORM

Although **Neisser** and **Plato** in working with trichophytin in human beings in 1902 had shown that in addition to a general reaction a local one was often produced in ringworm cases at the seat of inoculation, it was not till some years later that investigations were carried out by several observers as to the nature of these local reactions.

Bloch, and **Bloch** with **Massini,** as already mentioned, obtained on reinoculation in animals and men who had suffered from deep-seated tinea, a modified lesion which ran a rapid course. This they rightly attributed to the fact that the skin was allergic to the fungus. They also showed that in man every deep tinea leads to a heightened sensitiveness, which was shown by a positive cutaneous reaction to filtrates of ringworm cultures. The reaction is exactly analogous to the Pirquet reaction with old tuberculin in tuberculosis. **Bloch** found that it appeared in 7–8 days after first inoculation with the disease and remained long after the disease is healed (up to 3 years). It occurs both after injection of living fungi and after inoculation with culture filtrates. **Amberg** in 1910 did a number of cutaneous tests with trichophytin, and pointed out the far-reaching analogy between the cutaneous trichophytin reaction and the tuberculin Pirquet reaction. Both may persist for a long time after the active disease has ceased to exist, indicating that the infection has left the body in a state of altered reactivity or allergy. He

found that a person who had had a deep tinea 29 years previously still gave a positive cutaneous reaction with trichophytin. He thinks that the skin test may be of value in diagnosis, but in view of the fact of its long persistence after the disease is healed, as with the tuberculin Pirquet reaction, a negative reaction may be of greater value than a positive one, thus enabling one to exclude ringworm. He suggests its value to distinguish the circinate syphilides of the face from ringworm.

Amberg also in one case tested with trichophytin obtained, as is sometimes seen in tuberculin Pirquet tests, a delayed reaction on the 8th day. This he considers as analogous to the so-called accelerated reaction in cases of revaccination against smallpox. The explanation is that the organism has an insufficient amount of antibody at its disposal with which to react immediately. The injection of the trichophytin leads to a renewed formation of antibody which later reacts with the trichophytin still left at the seat of injection. **Bloch** obtained regularly positive skin reactions to trichophytin in cases of kerion and tinea barbæ. The degree of reaction was proportionate to the intensity of the infection. The deeper and more inflamed it was, the greater the reaction. Very superficial tineas gave a slight or no reaction. There was no reaction in cases where only the nails or hair were affected. That is what one would expect, because in the latter cases the fungus is growing more as a saprophyte on the surface than as a parasite in the tissues.

Hanawa did intracutaneous tests in animals immune from previous inoculation with ringworm and found that positive results were obtained. The reaction was similar to that produced by reinoculation with living fungus, viz. a marked partly necrobiotic inflammation which occurs as a nodule in the centre with a surrounding inflammation. **Kusonoki** did both cutaneous and intracutaneous tests with trichophytin, and found the intracutaneous method is more certain than the cutaneous. He obtained positive results by the intracutaneous method both in deep-seated and superficial cases. After intracutaneous injection in deep trichophytosis the temperature usually rose to 39·8° C., but not in superficial ringworm. Trichophytin produced a stronger reaction, the more virulent the kind of fungus used to

make it. The older the broth culture of ringworm, the more potent is the trichophytin produced. Ringworm cases usually gave a positive reaction with "favin," but the reaction was weaker in ringworm than in favus, and favus cases seldom reacted positively to trichophytin. By this method it was found that mouse favus (*Achorion Quinckeanum*) stands nearer to the ringworm fungi than human favus (*Achorion Schönleinii*). Repeated intracutaneous injection leads to a gradual weakening of the reaction.

The reaction was found to be always negative in other diseases and in normal persons. In immune animals it is irregular, and in normal animals sometimes positive. In cachectic and young animals it is always absent.

Sutter also did cutaneous and intracutaneous tests with trichophytin made from Achorion Quinckeanum. For the intracutaneous test he injected 0·1 c.c., maltose broth being used as a control. He did the control, cutaneous, and intracutaneous tests side by side, and obtained rather astonishing results in 150 healthy persons: 123 being positive and 27 negative by the intracutaneous test. In 5 cases only was the cutaneous test weakly positive, and that in the cases which gave very strong positive intracutaneous tests. Other observers have obtained positive skin reactions in normal persons. **Amberg** reports 4 cases and **Kusonoki** 1. In these cases no previous history of ringworm was to be obtained.

Sutter thinks that the intradermal reaction to 0·1 c.c. trichophytin can produce a certain degree of reaction which can only be quantitatively distinguished from a specific trichophytin reaction. The question is whether all those apparently normal individuals had had an attack of some mycotic disease previously. **Amberg's** case, giving a positive reaction 29 years after a deep tinea, shows that the reaction may persist for a long time, but it is not at all probable that all these persons could have had some form of tinea in childhood without knowing it. Another and more likely explanation is that the reaction is not a specific trichophytin reaction but a general antigen one. As **Sutter** points out, trichophytin is not a pure substance, and the reaction might be due to traces of the peptone and maltose in which the fungus was grown. It might be analogous to the agar reactions

to be referred to later on. That it is a quantitative rather than a qualitative reaction is shown by the fact that dilution to 1 in 1000 gave far more marked reactions in ringworm cases than in healthy individuals.

These results would also tend to prove that the intracutaneous method is not suitable as a diagnostic test, and that the cutaneous is to be preferred as it is more specific.

Sutter also tested the degree of reaction at different age periods in healthy individuals—140 cases were tested, and it was found that the younger the individual the fewer positive reactions obtained. Infants hardly ever reacted at all. The majority of positive reactions were obtained between the ages of 15 and 65 years. **Sutter** thinks that the probable explanation is that given by **More** and **Feer,** who have shown that in the first years of life the faculty of reacting is almost absent from the skin. That is in accordance with what one would expect. The infant has not yet suffered from any infection, and its protective mechanism has not been stimulated, whereas in adults who have passed through various infections, their tissues have become sensitised to various chemical substances, bacterial and otherwise. As the intradermal trichophytin reaction has been shown to be a relatively non-specific one, one would expect a high percentage of positive results in adults who were already sensitised from attacks of various acute or chronic diseases.

This effect of acute and chronic diseases on the trichophytin reaction was specially studied by **Sutter.** He tested 13 cases of pneumonia, 4 of scarlet fever, 2 of measles, and 2 of typhoid fever, none of whom had previously had tinea, and found that the intradermal trichophytin reaction was negative in all during the fever, but later on all gave positive reactions. He also quotes **Pecori,** who tested with trichophytin injections 6 cases of ringworm who had measles. They were all negative at the height of the disease and while the rash was out, but later on were positive. This corresponds with what has been known for some time regarding the tuberculin Pirquet test in measles and other fevers. **Pirquet, Hamburger,** and **Rollys** found that the tuberculin Pirquet, if present before, disappeared during the attack of these fevers and returned again later on recovery.

Hamburger likewise found that there was a marked diminution of the reaction to vaccinia during measles. **Pirquet** attributes the temporary loss of the reaction during fevers to the temporary absorption of the antibodies to tuberculosis. **Sutter** also did a number of trichophytin tests in chronic diseases, and found that in arthritis, chronic nephritis, tuberculosis, diabetes, arteriosclerosis, carcinoma, endocarditis, pernicious anæmia, gastritis, tabes dorsalis, and gonorrhœa, the reaction is practically the same as in healthy individuals, except that in cachectic patients it is absent. In 3 cases of hemiplegia the reaction was much weaker on the paralysed than on the other side. These results also are what one would expect, as in all these infections and toxæmias the tissues are already sensitised, and as the reaction persists during a chronic infection and long after its disappearance, practically everyone on reaching adult age will react. The absence of the reaction in cachectic cases also corresponds to the well-known fact that the tuberculin skin tests disappear in the late cachectic stages of tuberculosis.

Scholtz, like **Sutter,** did numerous intradermal tests with trichophytin (**Höchst**). He used it in dilutions of 1 in 50 and 1 in 100. Positive reactions occurred within 24 hours, producing a slightly raised flat papule with a halo of erythema about the size of a sixpence. Smaller areas of erythema, even although slightly papular, were considered negative. He found that non-specific reactions occurred with these dilutions, but not sufficiently frequently to interfere with the value of the test. Cases of lupus vulgaris reacted almost without exception positively, but patients with tuberculosis of the lung did not react positively. The reaction in lupus was so constant that **Scholtz** considers it useful in distinguishing between lupus and tertiary syphilis, which does not give the reaction.

Fuhs, using a trichophytin produced by previously digesting a culture of trichophyton, found that 4 cases of superficial and 8 of deep ringworm were all negative to the cutaneous Pirquet test. But by the intracutaneous method in superficial forms of ringworm the results were negative, and in deep cases a positive reaction was obtained, beginning in 6–12 hours, reaching its height in 24–48 hours, and slowly fading leaving pigmentation.

Pederson did a number of experiments to see if the cutaneous

trichophytin reaction was more marked on areas where trichophytides (see later) had been present. He assumed that the skin in such areas should be more sensitive to trichophytin than in other areas. Nine cases of kerion without secondary trichophytides were tested by Pirquet's method on the abdomen, upper arm, and leg in each case. All were positive on the abdomen, some of them markedly so; 7 were positive on the arm, and 4 on the leg. **Pederson** therefore concludes that trichophytin tests should always be done on the abdomen near the umbilicus. Now that is the region where trichophytides are most constantly found. He also tested similarly 6 cases of kerion with secondary trichophytides. All were positive on the abdomen and upper arm, *i.e.* where the trichophytides were present, and only 2 were positive on the leg, where there were no trichophytides.

In order to see whether the skin round a lesion was more sensitive than elsewhere, 4 cases of kerion were Pirqueted near to and at a distance from the lesion. He found that the reaction was always stronger on or around areas near the lesion where secondary superficial tinea lesions had been or were. **Sutter** repeated these experiments and obtained the same heightened reaction around the ringworm lesions. He also inoculated cases with living fungus both in the neighbourhood of the existing lesion and at a distance, and found that he obtained an early reaction with a papular eruption, with a rapid disappearance of fungus from the area, and later the lesion became spinulous, but no actual trichophytosis developed. In areas at a distance a typical early reaction was absent, and a short-lived trichophytosis developed, showing that the skin in these areas was not so sensitised as it was near the lesions.

A great many intradermal trichophytin tests were also performed recently by **Arnold,** both in healthy children and children with ringworm. In 130 healthy children with no previous history of ringworm, 14 gave positive reactions to a polyvalent trichophytin (**Höchst**) diluted 1 in 10. Forty-one cases of ringworm were also tested. With trichophytin (1 in 100) no healthy children and 58 per cent. of children with superficial tinea reacted. The age of the child (up to 14 years) had no influence on the specific reaction. **Arnold** found, when the reaction

did occur, no difference in intensity or duration between the non-specific reaction in healthy children and the specific reaction in ringworm cases. He agrees with **Sutter** that the difference between specific and non-specific reactions is a quantitative one only, and if the results are to be of any value the trichophytin must be diluted to between 1 in 50 and 1 in 100. He could find no special difference between the reactions in deep and superficial tineas. Many superficial forms (tinea capitis) gave more marked reactions than the deep.

He also found that feverish diseases such as measles and varicella cause an absence of the specific reaction. The non-specific reaction with high concentrations of trichophytin was diminished, and with lower concentrations disappeared in measles, scarlet fever, diphtheria, and typhoid fever. The reaction to injection of carbolic acid, distilled water, and hypertonic salt solution injections, analogously to the fungus reactions, were also found to be diminished in fevers; so also the reaction due to trauma from injection of 0·2 c.c. of fluid into the skin. Cachexia either diminishes or prevents the reactions to trichophytin, carbolic acid, or trauma. Daily intracutaneous trichophytin reactions in ringworm cases caused a diminution in the degree of reaction. In small-spored ringworm of the scalp there was at first an increase in the reaction. This **Arnold** attributes to the fact that all cases were epilated by X-rays. This increased reaction is later followed by a diminished one. **Arnold** concludes that trichophytin is less specific than tuberculin. It shows a greater toxicity and a greater dependence on the condition of the skin. But he thinks it is more specific than the non-specific bacterial toxins, such as typhoid and diphtheria toxins, etc.

CUTIREACTIONS IN FAVUS

In favus capitis **Bloch** found the cutireaction to trichophytin (from Achorion Quinckeanum) almost always negative. The Achorion Schönleinii has no great power of allergising, and, therefore, human favus is a chronic disease and does not tend to heal spontaneously.

Kusonoki also found that favus cases seldom react positively to trichophytin, but favus cases always and ringworm cases

sometimes react positively to favin made from Achorion Schönleinii. These results again point to *Achorion Quinckeanum* (mouse favus), which has been so much used to produce trichophytin, being much more nearly related to the ringworm than the favus fungi.

Recently **Stein** did intradermal tests with a mixed polyvalent trichophytin (containing 6 kinds of trichophytons and 3 achorions) diluted 1 in 10. Fifty-one cases of favus capitis, all due to Achorion Schönleinii, were all negative even although the trichophytin contained one-ninth part of Achorion Schönleinii. Similarly, 17 cases of favus corporis (12 with scutula), all due to Achorion Schönleinii, all showed negative cutireactions, but 2 cases of favus corporis due to Achorion violaceum both reacted positively. One case of favus corporis due to Achorion Quinckeanum and another due to Achorion gypseum both reacted positively.

Therefore out of 67 cases of favus, only 4 reacted positively, and these 4 were all due to animal achorions. **Stein** thinks that one must make a distinction between the Achorion Schönleinii of human favus and other achorions. He suggests that the Achorion Schönleinii has, in the course of centuries, become accustomed to the human skin, always being transmitted from man to man; whereas the other achorions are normally animal parasites, and, if they infect man, set up an immunising process which causes a skin allergy and a tendency to spontaneous cure such as never occurs in human favus.

AUTHOR'S EXPERIMENTS WITH CUTIREACTIONS TO FUNGUS EXTRACTS

In 1909 I undertook some experiments to see whether a skin test could not be obtained for diagnostic purposes in cases of tinea and favus capitis. As the results were disappointing, they were not published at the time. It is, however, thought advisable that they should be recorded. Extracts of the fungus were made in the following manner :—

1. *Extracts* from a small-spore fungus=*Microsporin.*

A pure culture of microsporon Audouini from a case of tinea capitis was used. With this culture an Erlenmeyer's flask,

containing liquid 4 per cent. maltose peptone medium, was inoculated. It was kept at room temperature. In 3–4 weeks' time the surface of the medium was covered with a pellicle of fungus which gradually increased in density and thickness. Growth was allowed to go on for 9 months, when the mass of fungus was removed and dried in the oven in a sterile Petri's dish. It weighed 1·135 grm. In the dry state it was pounded in a mortar as finely as possible, and 15 c.c. sterile saline added, and the masses of fungus again crushed in a mortar. The fluid mass was filtered through sterile filter paper and the slightly turbid filtrate containing any soluble toxins labelled *Microsporin B.* The residue containing the undissolved mass was mixed with other 15 c.c. sterile saline and labelled *Microsporin C.* Microsporin B and C were both sterilised by heating at 65° C. for 1 hour. Twenty drops of 1 in 20 carbolic were then added. Cultures were made from both preparations on Sabouraud's proof medium and found to be sterile.

By the above means 2 microsporins were obtained :—

Microsporin B containing any soluble toxin.

Microsporin C containing the dead crushed mycelium and spores.

2. *Extracts* from large-spore fungus= *Trichophytin.*

As in the case of the small-spore fungus, cultures were made on liquid maltose peptone medium and allowed to grow at room temperature for 4 months. Two varieties of large-spore fungus were used—a Trichophyton acuminatum from a patient named Richardson and a Trichophyton crateriforme flavum from a patient named King. Both were treated similarly. The felted mass of fungus was taken from the surface of the medium and the subjacent fluid filtered through sterile filter paper. The filtrate which contained any soluble toxin which had been dissolved out into it during the process of growth of the fungus was labelled *Trichophytin A.*

The mass of fungus was then washed in sterile saline and pounded up in a mortar with 20 c.c. sterile saline and filtered through sterile filter paper. The filtrate which contained any soluble toxin obtained by crushing the fungus was labelled *Trichophytin B.* The residue consisting of the crushed masses

of fungus was again, more thoroughly than before, pounded in a mortar, mixed with 15 c.c. sterile saline, and labelled *Trichophytin C*. All three preparations of trichophytin were sterilised for 1 hour at 65° C., and to each 20 drops of 1 in 20 carbolic acid added, and cultures made to test their sterility.

Thus 6 trichophytin extracts were obtained, viz. :—

Trichophytin A (Richardson).
Trichophytin B ,,
Trichophytin C ,,
Trichophytin A (King).
Trichophytin B ,,
Trichophytin C ,,

3. *Extracts* from *favus* fungus=*Favin.*

A typical culture of Achorion Schönleinii was inoculated on liquid maltose peptone medium and allowed to grow for 4 months. The same procedure as in the preparation of the trichophytin extracts was followed, and *Favin A*, *Favin B*, and *Favin C* obtained.

Favin A contained the soluble toxin in the liquid medium.

Favin B contained the soluble toxin in the liquid after crushing the fungus.

Favin C consisted of the crushed mass of fungus.

With the above 2 preparations of microsporin, 6 of trichophytin, and 3 of favin, cutaneous tests were done as in Pirquet's tuberculin test. The tests were all done on the left upper arm. Three small scratches were made with a needle and across these 3 similar scratches and a drop of the fungus extract rubbed gently in with a glass rod. Controls were done in every case using liquid peptone maltose medium with the addition of 5 per cent. carbolic acid. The arms were examined at intervals of 24 hours for 4 days.

The following tables give the results, + indicating a positive, − a negative, and ± a doubtful reaction.

[Table.

Sex.	Age in Years.	Disease.	Date.	Extract used.		Result in Days.			
						1.	2.	3.	4.
M. . .	7	Tinea cap. (small spore).	July 22, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	+	+	+
					M.C.	−	+	+	+
M. . .	11	Tinea cap. (small spore).	July 22, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	−	−	−
					M.C.	−	−	−	−
F. . .	8	Tinea cap. (small spore).	July 23, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	±	±	±	−
					M.C.	±	±	±	−
M. . .	9	Tinea cap. (small spore).	July 24, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	±	±	−	−
					M.C.	±	±	−	−
M. . .	11	Tinea cap. (small spore).	July 24, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	−	−	−
					M.C.	−	−	−	−
M. . .	7	Tinea cap. (small spore).	July 26, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	±	±	−
					M.C.	−	±	±	−
F. . .	5	Tinea cap. (small spore).	Aug. 4, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	±	±	−
					M.C.	−	±	±	−
F. . .	3	Tinea cap. (small spore).	Aug. 4, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	−	−	−
					M.C.	−	−	−	−
M. . .	6	Tinea cap. (small spore).	Aug. 10, 1909.	Microsporin B and C.	Control	−	−	−	−
					M.B.	−	−	−	−
					M.C.	−	−	−	−

Sex.	Age in Years.	Disease.	Date.	Extract used.		Result in Days.			
						1.	2.	3.	4.
M. . .	7	Tinea cap. et corp. (small spore).	Aug. 10, 1909.	Microsporin B and C.	Control	—	—	—	—
					M.B.	—	—	—	—
					M.C.	±	±	—	—
M. . .	14	Tinea cap. (small spore).	Aug. 24, 1909.	Microsporin.	Control	—	—	—	—
					M.B.	—	±	±	—
					M.C.	—	—	±	—
F. . .	9	Tinea cap. (large spore) (kerion).	July 23, 1909.	Trichophytin (King) A, B, and C.	Control	—	—	—	—
					T.A.	—	—	—	—
					T.B.	—	±	±	—
					T.C.	—	±	±	—
M. . .	11	Tinea cap. (large spore).	July 24, 1909.	Trichophytin (Richardson) A, B, and C.	Control	—	—	—	—
					T.A.	—	—	—	—
					T.B.	—	—	+	—
					T.C.	—	—	—	—
M. . .	11	Tinea cap. (large spore).	July 26, 1909.	Trichophytin (Richardson) A, B, and C.	Control	—	—	—	—
					T.A.	—	—	—	—
					T.B.	—	—	—	—
					T.C.	—	—	—	—
F. . .	4	Tinea cap. et corp. (large spore).	July 26, 1909.	Trichophytin (Richardson) A, B, and C.	Control	—	—	—	—
					T.A.	—	—	—	—
					T.B.	—	—	—	—
					T.C.	—	—	—	—
M. . .	59	Tinea barbæ (large spore).	July 23, 1909.	Trichophytin (King) A, B, and C.	Control	—	—	—	—
					T.A.	—	—	—	—
					T.B.	±	±	—	—
					T.C.	±	±	—	—
M. . .	39	Tinea barbæ et corp. (large spore—ectothrix).	July 27, 1909.	Trichophytin (King) A, B, and C.	Control	—	—	—	—
					T.A.	—	—	—	—
					T.B.	—	—	—	—
					T.C.	—	—	—	—
M. . .	12	Tinea corp. (large spore).	July 26, 1909.	Trichophytin (Richardson) A, B, and C.	Control	—	—	—	—
					T.A.	—	±	±	±
					T.B.	—	±	±	±
					T.C.	—	±	±	±

Sex.	Age in Years.	Disease.	Date.	Extract used.		Result in Days.			
						1.	2.	3.	4.
M. . .	7	Favus cap.	July 22, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	−	−	−	−
					F.B.	−	−	−	−
					F.C.	−	−	−	−
F. . .	9	Favus cap.	July 22, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	−	−	−	−
					F.B.	−	−	−	−
					F.C.	−	−	−	−
M. . .	10	Favus cap.	July 23, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	±	−	−	−
					F.B.	−	+	+	±
					F.C.	+	+	−	−
M. . .	11	Favus cap.	Nov. 2, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	±	±	±	−
					F.B.	±	±	±	−
					F.C.	±	±	±	−
M. . .	8	Favus cap.	Nov. 2, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	−	−	±	−
					F.B.	−	−	−	−
					F.C.	−	−	−	−
M. . .	6	Favus cap.	May 11, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	−	−	−	−
					F.B.	−	−	−	−
					F.C.	−	−	−	−
F. . .	7	Favus cap.	May 2, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	−	−	−	−
					F.B.	−	−	−	−
					F.C.	−	−	−	−
M. . .	6	Favus corp.	Aug. 2, 1909.	Favin A, B, and C.	Control	−	−	−	−
					F.A.	−	±	−	−
					F.B.	−	±	−	−
					F.C.	−	±	−	−

From these tables it will be seen that in 11 cases of ordinary small-spore tinea capitis all due to Microsporon Audouini, in 4 the results are absolutely negative. In 6 doubtful reactions were seen, and those were considered as probably negative. In judging the reaction, no reaction was considered positive unless a definite papule was formed with an area of erythema around it at least twice the size of the control. Five of these doubtful reactions occurred to both microsporin B and C, and in 1 to microsporin C only. In 1 case only was there a definite positive reaction to both microsporin B and C.

In 3 cases of ordinary tinea capitis due to large-spore fungus tested with trichophytin A, B, and C (Richardson) all were completely negative. One of these cases, in addition to having tinea capitis, also showed small lesions on the body.

One case of inflamed large-spore tinea capitis (kerion) tested with trichophytin A, B, and C (King) gave a doubtful reaction to trichophytin B and C.

One case of large-spore tinea corporis also gave doubtful reactions to trichophytin A, B, and C (Richardson).

In 2 cases of tinea barbæ due to large-spore fungus, one of which also had tinea corporis, the latter was negative and the former gave doubtful reactions to trichophytin B and C.

Seven cases of favus capitis, all due to Achorion Schönleinii, were tested with favin A, B, and C, and 4 were negative, 2 doubtful, and 1 positive. Similarly, 1 case of favus corporis due to Achorion Quinckeanum gave a doubtful reaction to all 3 forms of favin.

Therefore, out of 26 cases tested, only 2 (8 per cent.) gave positive cutaneous reactions, 1 ordinary small-spored tinea and 1 ordinary favus capitis. Thirteen were definitely negative and 10 doubtful, but I think the doubtful cases should also be considered as negative. The summarised results are shown in tabular form on p. 136.

These results are rather disappointing, but agree to some extent with **Sutter,** who only obtained 5 positive reactions in 150 cases tested (*i.e.* nearly 4 per cent.) by the cutaneous method. They, however, do not agree with the results of **Bloch, Amberg, Sutter,** and others in so far as my 1 positive case in ringworm was in an ordinary small-spored tinea capitis, and

negative results were obtained in all the suppurating cases such as kerion and tinea barbæ.

Kind of Case.	Number of Cases tested.	Negative.	Doubtful.	Positive.
Small-spore tinea capitis .	11	4	6	1
Large-spore tinea capitis .	3	3	0	0
Large-spore tinea capitis (kerion) . . .	1	0	1	0
Large-spore tinea corporis .	1	1	0	0
Large-spore tinea barbæ .	2	1	1	0
Favus capitis . . .	7	4	2	1
Favus corporis . . .	1	0	1	0
Total . . .	26	13	11	2

A positive reaction in 1 case of favus capitis out of 7 cases (*i.e.* about 8 per cent.) is more than was usually obtained by **Bloch, Kusonoki,** and others. Also the 1 case of favus corporis tested was doubtful and probably negative, even although it was due to Achorion Quinckeanum and was spreading rapidly. The fact that my favin was made from Achorion Schönleinii and not Achorion Quinckeanum may have had something to do with the result. No great difference was found between the reactions to A, B, and C extracts of fungus. On the whole, the A extracts (*i.e.* toxins in fluid medium before fungus crushed) gave very few even doubtful reactions, whereas the B extracts (*i.e.* toxins in fluid medium after crushing of fungus) and the C extracts (*i.e.* masses of crushed fungus) in practically all cases gave similar results. My microsporin B, trichophytin B, and favin B corresponded to the trichophytins used by other workers and also to old tuberculin, and therefore, in comparing my results with those of others, the reactions to the B extracts were those which were adopted.

TRANSPLANTATION EXPERIMENT IN RINGWORM

A most interesting experiment was performed by **Bloch** in order to see whether in a sensitised person the sensitiveness was in the skin cell itself or not. A man with a chronic leg ulcer, which

TINEA BARBÆ.

required skin grafting, was made use of. Two pieces of skin were grafted on to the ulcerated area, the one a piece of **Bloch's** own skin, the other a piece of skin from a man who had never had ringworm and whose skin gave no cutaneous reaction to trichophytin. **Bloch** had previously infected himself with a deep tinea, and he gave a well-marked cutaneous reaction to trichophytin. After the 2 pieces of skin had "taken" and the ulcer healed, cutaneous tests with trichophytin were done on a healthy area of skin and also on the 2 grafted pieces of skin. The only area which reacted was the area where **Bloch's** own skin had been grafted. The other 2 areas gave no reaction at all.

This experiment is most important as it demonstrated that the sensitiveness belonged to the skin cell itself, and when that cell was implanted on a non-sensitive individual, it still retained its sensitiveness. This will be referred to again later on, when the mechanism of the cutaneous tests is discussed.

THE EFFECT OF RINGWORM AND FAVUS FUNGUS ON TISSUES OTHER THAN THE EPITHELIUM AND HAIRS

In cases of superficial tinea corporis and ordinary tinea capitis the fungus grows on the epithelium and hairs. Very little reaction is produced, and microscopically a slight small-celled infiltration or no infiltration at all is observed. But whenever the fungus gets more deeply into the tissues, either into the true skin or deeper, a much more marked reaction takes place. This has been long recognised in the inflamed ringworms such as kerion and tinea barbæ (Plate opposite) where large lumpy lesions are present. A good deal of experimental work has been done to show the result of infecting the body with various fungi. As far back as 1870 **Semmer** injected the spores of penicillium mixed with distilled water into the jugular veins of animals, but on killing the animals later no lesions were found. But in 1885 **Naegeli** found that injection of fungi into animals led to the formation of granulomatous masses with giant cells in the internal organs. Similar lesions have long been known to occur in infections with actinomycosis, and more recently cases of sporotrichosis were published and in these infections large granulomata were demonstrated as the result of the invasion of the fungus.

Similarly, when the ringworm fungus gets out of the hair follicles into the true skin, a marked reaction takes place with suppuration. These swollen areas, if excised, were found by **Forlanini, Pellizari,** and others to show a mass of round cells, together with abundant giant cells such as are seen in all the granulomata. Those kerion cases are much more commonly due to a large-spore fungus, but **Sabouraud, Lewandowsky,** and others have described kerion due to Microsporon Audouini. In Edinburgh kerion is a fairly frequent condition, and it is not at all rare to find it due to the small-spore fungus.

Tinea barbæ also in the deep-seated form with pustules and large raised bluish-red lesions also shows this same granulomatous formation.

These conditions (kerion and tinea barbæ) have been known clinically for a long time, but there is another type of lesion which is very much rarer, viz. granuloma trichophyticum. This condition was first described in 1883 by **Majocchi** in Italy. Most of the cases have been recorded in Italy. **Majocchi, Vignolo-Lutati, Sorrentino, Pini, Mazza, Chirivino,** and **Campana** have all reported cases. The only case recorded in this country was one by **Sequeira** in 1912. The condition is quite distinct from kerion. It is characterised by dermic, rounded, indolent swellings which are painful or tender and covered with normal or slightly red skin. The lesion is not scaly, is of elastic consistence; usually the centre softens, fluctuates, and may burst on the surface leaving a chronic indolent ulcer. Microscopically it shows all the characteristics of a subcutaneous granuloma with plasma cells, epithelioid and giant cells. **Majocchi** found that this granulomatous lesion might be due to different kinds of fungus such as Trichophyton violaceum, Tr. rosaceum, Tr. cerebriforme, and Tr. plicatile, but was usually due to Tr. violaceum. **Mazza** and **Sabouraud** each found the Tr. violaceum in 1 case, **Pini** found a trichophyton with a yellow powdery culture which **Sabouraud** thinks was Tr. cerebriforme or regulare; and in another case **Pini** obtained a snow-white culture, probably Tr. gypseum. Therefore this peculiar formation is not due to any special kind of fungus causing a special kind of lesion.

Sequeira's case in this country was a peculiar one, in a boy

aged 14 who had suffered from tinea corporis for 8 years. His sister, aged 21, had also been affected with the same disease for 15 years. The boy, when the disease first started, had no treatment. The disease gradually spread till the whole trunk and parts of the limbs were affected with a scaly brownish eruption which, on close inspection, showed raised red papules in rings. The finger nails were all rough, thickened, and opaque. The eruption itched a good deal. A year after he became affected a swelling appeared near the umbilicus. This broke down and formed an ulcer. This ulcer healed under treatment, but broke down again and began to enlarge. When seen by **Sequeira** the boy had a reniform ulcer near the umbilicus 3 inches by $1\frac{1}{2}$ inch with thickened indurated margins and undermined edges. The base was covered with a moist yellow-brown slough. There was a thin yellowish purulent discharge. On the right wrist was a circular infiltrated patch the size of a penny which had never ulcerated and resembled a local tuberculous infection. Scrapings from the scales and nails and the exudate from the ulcer near the umbilicus all yielded pure cultures of a fungus which was identified by **Sabouraud** as Trichophyton plicatile. There seemed little doubt that the ulcer was caused by the fungus. The boy was in hospital for nearly 2 years, and during that time a very large number of flat, buttonlike lesions varying from 2 to 2·5 cm. in diameter developed. Many of these were cured by the injection of carbolic acid. Some were scraped away and strong antiseptics applied to the base. Iodine, chrysarobin, and many other antiseptics were used for the skin lesions, and finally they all cleared up, the umbilical ulcer healing after prolonged immersion in a boracic-acid bath. The nails were all removed and the nail-bed dressed with weak iodine solution. The granulomatous eruption left extensive scars. At no time was the hairy scalp affected except when the disease extended from the left auricle, which showed a raised lesion which led to considerable sloughing.

The boy remained well for 3 years except for the nail lesions. These were again treated but not cured, and after another 3 years he had a fresh outbreak of granulomata with dry, scaly areas of skin as before. He had extensive lumpy lesions in right axilla and left groin. The reinfection was probably from the

finger nails. Microscopically the tumourlike lesions showed giant cells, lymphocytes, plasma, and eosinophile cells. Filaments of fungus were seen in the giant cells.

Sequeira, on discussing the case, expresses the view that "it is rather curious, considering what is known of the granulomata caused by sporotrichia and other allied fungi, that granulomatous reactions are not more common from trichophytic infection." He also suggests that it may be difficult for the trichophyta to develop deeply in the tissues.

Mazza did experiments by injecting cultures of ringworm and hairs with ringworm subcutaneously into man and animals. He succeeded in producing granulomata which were the very same as those produced when foreign bodies are introduced into the tissues.

As in ringworm, so in favus a deep infection may occur. **Majocchi** first described kerion due to favus in 1877. **Truffi** found that the Achorion Schönleinii may determine a morbid lesion identical clinically with kerion, and also that it may produce in the skin of man and in the subcutaneous tissues of the guinea-pig a granuloma analogous to that produced by the trichophytons. **Bukowski** in 1900 injected achorion intravenously into rabbits and produced in the lungs nodules with a granulomatous structure with giant cells. In these giant cells were portions of the fungus. He also found that favus and trichophyton fungi, if injected intraperitoneally, produced pseudo-tuberculous nodules. The fungus is phagocyted by the cells and often causes necrosis of the cell. The same results were obtained by injecting dead as by injecting living fungus. **Bukowski** doubts whether these results were due to the toxins of the fungus, because no lytic substances were found in the peritoneal exudate. He suggests that the whole reaction might be a mechanical one due to pressure or the result of the introduction of a foreign body.

Sabrazes previously in 1893 had produced very similar lesions by injection of fungi, but **Carini** obtained no results by injecting rabbits intravenously with achorion. **Quincke** in 1886 produced nodules in the lungs of rabbits by injecting Achorion Schönleinii intravenously. These nodules were found to contain the fungus.

Radaeli also confirmed this work. A pure culture of Achorion Schönleinii inoculated into the vein of a rabbit caused the

formation of nodules in the lung. These nodules microscopically were granulomata with areas of necrosis. In the centre of these nodules masses of fungus with radiating filaments, resembling what is seen in actinomycosis, were found. Similar lesions were also found to be produced in the lung by intravenous injection of Trichophyton violaceum.

More recently, in 1910, **Darier** and **Halle** reported a case of favus capitis which clinically showed no peculiarity, but on excising a piece of skin with scutula, pseudo-tuberculous nodules with giant cells were found in the corium. This case they describe as a " granulome favique."

From these observations, therefore, there seems no doubt that both trichophytosis and favus may in certain cases lead to a granulomatous formation. These formations are similar to those seen in tubercle, syphilis, sporotrichosis, etc. They are to be looked upon as reactions to the invasion of the fungus in individuals who are sensitised to the infections, and as they can be produced equally well with dead as with living fungus, they are analogous to the reactions produced by subcutaneous injections of tuberculin in tubercle-sensitive individuals. Whether the fungus spreads by local growth in the skin or is carried to the skin by the circulation, there is no evidence one way or the other to show ; but it is a question whether they should not be regarded more as large " trichophytides " analogous to the lesions in **Bazin's** disease or the gumma in tertiary syphilis. Both of these latter conditions contain the causal organisms in small numbers, and the relatively large lesion is due to the patient being highly sensitised to the infection, thus leading to a marked reaction.

THE TREATMENT OF RINGWORM AND FAVUS WITH FUNGUS EXTRACTS

It has already been shown that **Neisser** and **Plato, Bloch** and others obtained local and general reactions by injection of trichophytin. From that it is natural to assume that results might be obtained by trichophytin injections in the treatment of ringworm.

Bloch succeeded by giving injections of trichophytin in causing the healing of a case of ringworm without any local treatment.

He also, in a case of kerion due to Trichophyton rosaceum, succeeded in healing it by inoculating another healthy area of skin with Achorion Quinckeanum. These results were obtained in deep-seated lesions, but in the chronic superficial small-spore tineas and in favus he found that fungus injections did not cause healing.

Bruck and **Kusonoki** found that injections of trichophytin had no parasiticide effect on the fungus, but that they had a specific effect in stimulating the tissues to expel it. Whilst the lesion was fading, the fungus could still be found and cultivated. Therefore the effect of trichophytin was not to kill the fungus, but to make the tissues unsuitable for its growth. Three cases of deep-seated tinea barbæ, in which the cutaneous trichophytin test was negative and the intracutaneous test positive, were each cured in about 10 days by trichophytin injections. He found intracutaneous injection better than subcutaneous, as it avoided the general and other disturbances produced by subcutaneous injection. No focal reactions were seen. Two cases of superficial tineas were treated similarly but with no result.

These results show that in cases of ringworm where the patient is hypersensitive and gives a positive intradermal reaction, the intracutaneous administration of antigen at intervals assists the natural tendency to healing and results in a cure of the disease. Whereas, as already shown, injection of trichophytin will not sensitise an animal, but infection with the disease will. That therefore explains why trichophytin injections do not cure superficial tineas, because a sensitisation has not taken place.

In cases repeatedly treated with intracutaneous trichophytin injections, **Bruck** and **Kusonoki** found that the local reaction becomes weaker and weaker. On the other hand, **Stein** observed that every additional intracutaneous administration of antigen led to a local and focal reaction.

Stein points out that **Citron** has shown that the hyphomycetes form no toxins. Mice injected intraperitoneally or subcutaneously with filtrates of cultures of ringworm show no noteworthy disturbances, even in relatively large doses. Therefore we must conclude that the pathogenic fungi are not in a position to form an extra-cellular toxin. This is not surprising, as ringworm, even although it produces an intense skin lesion,

does not cause any general symptoms such as are seen in diphtheria and other infections with organisms which produce toxins. **Stein** argues therefore that extracts of the fungus and not filtrates should be used. Just as with attempts to produce immunity to ringworm, all strains of fungus do not immunise equally well, so all extracts do not act equally well. **Bruck** and **Kusonoki** used Trichophyton gypseum, but **Stein** found that the cultures were very thick and did not rub up easily. He obtained the best trichophytin from Achorion Quinckeanum. The effect of the treatment does not depend on treating the patient with the trichophytin from his own fungus, but on the preparation which is most richly saturated with the decomposition products of the fungus. This is the case in trichophytin prepared from Achorion Quinckeanum. Although the preparation is really a "favin," as already pointed out, the favuses and trichophytons are very closely related biologically.

Stein treated 15 cases of deep-seated ringworm. A diagnostic cutaneous test was done first to see whether the patient reacted promptly to trichophytin. The more marked this reaction the better the prognosis. Injections of 0·1 c.c. trichophytin were given intradermically every 10 days. Two such doses may be enough to effect a cure. Local and focal reactions were seen, and also reactions in previously injected areas. Out of the 15 cases treated 10 were rapidly cured without local treatment. Two were improved and 3 showed little tendency to heal. In these cases the cutaneous reactions were very feeble. Five cases of favus capitis were treated similarly. The local reactions were less than in the deep tineas and focal reactions were absent. Two children with favus corporis contracted from a cat and due to Achorion violaceum also reacted promptly to trichophytin treatment

Stein also used a trichophytin ointment for therapeutic purposes on the same principle as the Histopin ointment in staphylococcal infections used by **Wassermann, Ledermann,** and **Beck.** He used a 30 per cent. ointment of trichophytin in lanolin. **Kusonoki** had used a similar 10 per cent. ointment for diagnostic purposes, but obtained no reactions. **Stein** used his 30 per cent. ointment by local application to the lesions with good results. This ointment alone without trichophytin

injections was not successful in curing cases, but it was found to be very useful in preventing recurrences if the injections had been stopped too soon. He claims that tinea barbæ and kerion ringworms can be healed more quickly by intradermal injection of trichophytin and local application of trichophytin ointment. In superficial tineas, which do not react to trichophytin, he recommends the trichophytin ointment alone. He also suggests the use of trichophytin ointment for rubbing the heads of healthy children to prevent the spread of small-spore ringworm of the scalp during epidemics.

Scholtz found that both deep and superficial ringworms healed rapidly with repeated injections of trichophytin (**Höchst**) without any local treatment. Injections were given every 4–5 days, and the trichophytin was diluted 1 in 100. The best results were obtained by giving the trichophytin intradermally, and the dose was split up and given in 3–4 places, 0·1 c.c. being injected in each area.

Fuhs used a digested culture of trichophytin fungus analogous to **Joanovic's** tubercle bacillus preparation. Twenty-six cases of ringworm were treated with doses up to 0·5 c.c. Intradermal and subcutaneous injection were found to produce the same result. The treatment was beneficial in the deep forms of tinea barbæ. It assisted and shortened the healing process and acted similarly to **Bloch's** and **Scholtz's** trichophytin. The almost constant dry absorption of the infiltration of the lesions without outward sign was different from what occurs when other trichophytins are used.

Rozsavolgyi treated over 100 cases of ringworm, chiefly tinea barbæ, with injections of trichophytin. He used a dilution of 1 in 100, and at first gave the same doses as **Scholtz** in the same way intradermally, dividing the dose up into 3 and injecting $\frac{1}{3}$ into 3 different areas. Later he gave the undiluted trichophytin in the same way, and only diluted it for children with kerion and in cases where he got a very marked local or focal reaction. He also gave the injections every second day and sometimes daily. At first he often produced large œdematous painful swellings with hyperæmia and œdema at the seat of injection. But the results on the whole were favourable, and no important drawbacks were found to the method.

Trichophytin was also used fairly extensively by **Truffi** for

therapeutic purposes. He was disappointed in the results, and thinks its therapeutic value very slight, whereas its diagnostic value is quite definite. He used the trichophytin by subcutaneous injection to get a focal and general reaction, but a great drawback to the method was the marked local reaction produced at the seat of injection.

A somewhat modified form of inoculations with fungus elements was reported by **Persson.** The case treated was an extensive favus corporis on body, limbs, finger and toe nails. The disease had lasted for 23 years. There is no mention of the scalp being affected. Microscopically the scales from the lesions showed fungus, and cultures on agar contained Achorion Schönleinii and staphylococcus aureus. Cultures of this achorion in 80 parts sterile salt water together with 20 parts of a 5 per cent. solution of nucleinic acid were incubated for 72 hours and diluted with physiological salt solution to give a suspension representing 5 million individual segments or spores to each c.c. This was sterilised at 180° F. for 45 minutes. The patient received in all 77 inoculations, varying between 500 and 5000 million. At first injections were given daily, then twice a day, and later every second day. By the 27th day the disease was practically healed, and 6 months later the patient was still well. The opsonic index gradually rose from 0·3 to 3·6 in 35 days.

Last year **Novak** published the results of treatment of cases of ringworm with fungus extracts. He used two preparations.

1. Trichophytin prepared in the state Serological Institute in Vienna, and
2. "Trichon" prepared by Schering in Berlin, and consisting of a polyvalent trichophytin made according to the formula of Professor Bruck.

The injections were given subcutaneously and were found to be useful as an aid to the usual local treatment with 1 per cent. hot resorcin solution. In severe cases the injections hastened the cure. If used alone, they were found insufficient to overcome a ringworm infection. The trichophytin (Vienna) was found to be a weaker preparation than trichon (Berlin), but was easier to handle, and its administration caused less pain and less local

reaction. **Novak** recommends "trichophytin" for superficial infections and "trichon" for deep cases.

As having a bearing on this subject, mention must be made of the result of treating cases of deep tinea barbæ with a non-specific vaccine. **Loeb** treated 12 cases with injections of Leukogen (**Höchst**), which is a vaccine containing staphylococcus aureus and citreus. **Loeb** found that by intracutaneous injection of Leukogen and by rubbing it into the skin no reaction is produced. In all cases by subcutaneous injection an œdematous tender swelling was produced, but as it occurred in non-ringworm persons it has no significance. Focal reactions were frequently observed, especially after the 2nd to 4th injection. The cases received on the average 10 injections each of from 10 to 500 million every 3–10 days. All healed in a relatively short time without other treatment. In 8 cases of more superficial tineas similarly treated, 4 were cured, 1 improved, 1 left before treatment was finished, and 1 recurred in 14 days after apparent healing. **Loeb** thinks that deep tinea barbæ is due to the ringworm fungus and staphylococcal infection, and that therefore the vaccine acts specifically. I cannot agree with this view. Doubtless the lesions are contaminated with the staphylococcus, but the facts that no reactions were produced by intracutaneous injection, or rubbing into the skin produced no reaction, and the subcutaneous injection produced a non-specific reaction, are all in favour of the method acting non-specifically. **Loeb** also admits that the treatment has no immunising effect, as in many cases new spots appeared in the course of treatment, and recurrences occurred after apparent cure. Deep tinea barbæ also tends to produce its own immunity whether treated or not, and once the sensitising process has begun, it is quite likely that injections of any bacterial substance would stimulate that process, and therefore the results were probably similar to those produced by non-specific bacterial therapy.

AUTHOR'S EXPERIMENTS WITH MICROSPORIN

In 1915 I treated 5 cases of ordinary tinea capitis with microsporin prepared as already described (p. 129) from a culture of Microsporon Audouini. Details of the cases are as follows :—

Case 1.—R. P., age 7. Tinea capitis for 1 month. Several areas. Small-spore fungus found.

Aug. 23, 1915. Vaccine 0·5 c.c. microsporin.
,, 26, ,, ,, 1 c.c. ,,
,, 30, ,, ,, 1 c.c. ,,
Sept. 3, ,, ,, 1 c.c. ,,

No local reaction produced, but patient not looking well. General condition improved again as soon as injections stopped. Left without treatment, and on 22nd November 1915 fungus again found in hairs. Result, negative.

Case 2.—A. R., age 9. Tinea capitis for 3 weeks. Large area near crown 3″×4″ and small spot on right side of head. Small-spore fungus present.

Aug. 11, 1915. Vaccine 0·5 c.c. microsporin.
,, 16, ,, ,, 1 c.c. ,,
,, 19, ,, ,, 1 c.c. ,,
,, 23, ,, ,, 1 c.c. Diseased areas look dry and dusty.
,, 26, ,, Injection area on left arm swollen, red, and tender. No injection given.
,, 30, ,, Swelling on arm gone down. Vaccine 1 c.c. No spread of disease on scalp.
Sept. 2, ,, Suph. præcip. ʒii, Hydrarg. ammoniat. ʒi in lanolin and vaseline āā ʒi, started locally.
,, 7, ,, Vaccine 1 c.c. microsporin.
,, 14, ,, ,, 1 c.c. ,,
,, 17, ,, ,, 1 c.c. ,,
,, 21, ,, ,, 1 c.c. ,,
,, 24, ,, ,, 1 c.c. ,,
,, 28, ,, ,, 1 c.c. ,,
Oct. 1, ,, ,, 1 c.c. ,,
,, 5, ,, ,, 1 c.c. Each of the last 8 injections caused some local swelling and tenderness.
,, 12, ,, Vaccine 1 c.c. microsporin.
,, 15, ,, ,, 1·5 c.c. ,,
,, 26, ,, ,, 1 c.c. ,,
,, 29, ,, ,, 1·5 c.c. ,,

Nov. 1, 1915. Vaccine 1·5 c.c. microsporin.
,, 5, ,, ,, 1·5 c.c. ,,
,, 8, ,, Last injection area on back very sore, swollen, red, and tender to touch. All the previous 6 injections caused some swelling, especially the last one. Fungus found in hairs from scalp. The seats of previous injections in many cases swelled up after subsequent injections.
,, 15, ,, Swelling on back not so red.
,, 25, ,, Swelling on back almost disappeared. Local treatment with ointment only continued till 14th February 1917, when he was X-rayed. Finally cured on 29th November 1917.

Case 3.—R. T., aged 4. Tinea capitas for some months. Several areas all over scalp. Small-spore fungus found.

Aug. 23, 1915. Vaccine 0·5 c.c. microsporin.
,, 26, ,, Vaccine 1 c.c. Local treatment with sulphur and ammoniated mercury ointment.
Oct. 5, ,, Patient was not brought back till to-day. Mother reports that he had diarrhœa after the first 2 injections. Diarrhœa now well. Vaccine 1 c.c.
,, 26, ,, Vaccine 1 c.c.
,, 29, ,, ,, 1 c.c.
Nov. 1, ,, ,, 1 c.c.
,, 4, ,, Vaccine stopped, as mother reported diarrhœa recommenced as soon as vaccine injections were resumed. Local treatment only continued. Diarrhœa stopped again within 2 days of stopping vaccine. Case finally cured by ointment on 18th July 1916.

Case 4.—M. H., age 10. Tinea capitis for 2 years, chiefly on left side of head. Several areas. Small-spore fungus found.

Aug. 21, 1915. Local treatment with sulphur and ammoniated mercury ointment started.

Aug. 23, 1915. Vaccine 0·5 c.c. microsporin.
,, 26, ,, ,, 1 c.c. ,,
Sept. 9, ,, ,, 1 c.c. ,,
,, 13, ,, ,, 1 c.c. ,,
,, 16, ,, ,, 1 c.c. ,,
,, 20, ,, ,, 1 c.c. ,,
,, 27, ,, Mother reports that child getting very thin and not eating well. Vaccine stopped. Diseased hairs found on scalp. Case eventually cured on 6th November 1917, after X-ray treatment.

Case 5.—R. S., age 12. Tinea capitis for 3 weeks. Several areas scattered over scalp. Small-spored fungus found.

Sept. 2, 1915. Local treatment with sulphur and ammoniated mercury ointment started.
,, 3, ,, Vaccine 0·5 c.c. microsporin.
,, 7, ,, ,, 1 c.c. ,,
,, 14, ,, ,, 1 c.c. ,,
,, 17, ,, ,, 1 c.c. ,,
,, 21, ,, ,, 1 c.c. Spots on right side of scalp redder than formerly.
,, 24, ,, Vaccine 1 c.c. microsporin.
,, 28, ,, ,, 1 c.c. ,,
Oct. 1, ,, ,, 1 c.c. ,,
,, 5, ,, ,, 1 c.c. ,,
,, 12, ,, ,, 1 c.c. ,,
,, 26, ,, ,, 1 c.c. ,,
Nov. 5, ,, ,, 1 c.c. Disease still present on scalp. After the third and subsequent injections there was some local swelling and tenderness and in some cases sites of previous injections swelled up. As the patient ceased to attend the later history is not known.

As will be seen from the above, the results were very disappointing, and therefore the method of treatment was discontinued. The local reactions at the seat of injection were always very marked, and in most cases the seats of previous injections

reacted to subsequent ones. All injections were given subcutaneously into the back between the scapulæ. In no case was any focal reaction produced in the scalp lesion. At no time was any temperature seen; but as the cases were out-patients and only seen on the days injections were given, there might have been rises of temperature following the injections. In Cases 1 and 4 there was a distinct effect on the general health, and I think in Case 3 one must attribute the diarrhœa to the injections. My own impression is that the symptoms were possibly not due to the fungus elements in the microsporin but to traces of maltose and peptone which could not very well be eliminated in the preparation of the microsporin.

The only other references which I can find to the treatment of small-spored tinea capitis with a vaccine are an article by **Strickler** published in 1915, and a short report by **MacKenna** in 1923. In his article **Strickler** describes how he made his "microsporin." He lays great stress on the use of a vaccine containing the fungus elements themselves as he considers the failure of **Plato's** trichophytins was due to the culture suspension being filtered. When I made my microsporin, the great difficulty I found was to get the fungus elements separated from one another. The cultures formed a felted mass of fungus which it was very difficult to rub up so as to separate spores and mycelium into sufficiently small pieces to allow of injection with the syringe. **Strickler** got over this difficulty by rubbing up the culture growths with crystals of chemically pure sodium chloride. By this method all the elements became separated so finely that filtration was unnecessary. After rubbing up the cultures, the sodium chloride was diluted with sterile distilled water to the strength of normal saline. **Strickler** gave his vaccine in doses of 0·5 c.c. up to 4 c.c. As it was found to be no advantage to employ the larger doses, the usual dose varied from 1 to 2 c.c. Injections were given, at intervals of 3 days, in the back between the scapulæ or into the buttock. After 6 or 7 injections had been given, infiltrated areas appeared sometimes at the seat of injection. In one instance an abscess formed. In no case did he find any constitutional reaction. The number of injections varied from 7 up to 17 in number. Seven cases were treated, 6 of

which were ordinary cases of small-spored tinea capitis, and the other was a kerion (fungus not stated). Six were cured in about a month and 1 in 3 months without local treatment. Therefore, **Strickler** concludes that tinea capitis can be cured by vaccine, and suggests its use together with ordinary local treatment.

MacKenna, in his book on *Diseases of the Skin*, refers to work done by **De Jong** with a vaccine prepared from cultures grown on a pea-flower medium. Although it is not definitely stated, I infer that the extract was made from the microsporon, and that cases of ordinary small-spore tinea capitis were treated. **MacKenna** came to the conclusion that the treatment was of value both in preventing the spread of the disease and in shortening the duration of the treatment with ointments.

TRICHOPHYTIDES, MICROSPORIDES, AND FAVIDES

In 1912 a new light was thrown on our conception of the changes taking place in ringworm infections by the description of trichophytides by **Jadassohn.** He noticed on several occasions in children with kerion, especially in the healing stage, that there suddenly appeared small pale red follicular papules on the trunk. These resembled lichen scrofulosorum very closely, but did not react when rubbed with tuberculin, as lichen scrofulosorum always does. Occasionally the lesions showed small horny projections resembling the clinical picture of lichen spinulosus. **Jadassohn** named them lichenoid trichophytides, and this conception was further strengthened by the fact that by rubbing trichophyton fungus into the skin of children suffering from kerion exactly similar lichenoid eruptions, which remain for some time, are produced. **Jadassohn** considered the lichenoid eruption in kerion cases as due to external auto-inoculation and as a hypersensitive reaction analogous to lichen scrofulosorum, and because no fungus was found in the lesions he concluded that the reaction was probably due to the toxins of the fungus.

Since **Jadassohn's** publication, numerous similar cases have been recorded by **Guth, Saeves, Chable, Sutter, Bloch, Rasch, Pedersen, Herxheimer,** and **Koster, Pulvermacher, Ambrosoli, Arzt** and **Fuhs, Jessner** and **Williams.**

At first these eruptions were only described in cases of large-spored tinea and usually in deep-seated cases, but recently they have been described in cases of small-spored ringworm constituting the so-called microsporides, and in favus, the "favides."

In addition to the papular eruptions, several other kinds of eruption have been described, so that the trichophytides may be divided into several clinical types.

1. Papular eruptions, lichen trichophyticus or lichenoid trichophytides.
2. Vesicular trichophytides.
3. Pustular trichophytides (impetigo trichophytica).
4. Eczematoid trichophytides.
5. Scarlatiniform trichophytides (erythema scarlatiniforme trichophyticum).
6. Nodular subcutaneous trichophytides (erythema nodosum trichophyticum).
7. Erythema multiforme trichophyticum.

PAPULAR LICHENOID TRICHOPHYTIDES—LICHEN TRICHOPHYTICUS

This seems to be the commonest form of trichophytide, and the majority of cases reported by the authors already mentioned were of this type. The exanthem is characterised by the sudden appearance of numerous lichenoid papules of flat or conical form. The papules are disseminated over the skin of the trunk, on the extremities, and more rarely on the face, and generally, but not always, localised in association with the follicles. They are widely distributed and often arranged in groups. The lesions are pale red, bluish, or brownish in colour, and the apex of the lesion may show a small scale, crust, or pustule. They appear in crops, and may disappear rapidly or persist for weeks. If they are closely set together, a scaly area may be produced resembling a seborrhœic eczema (eczematoid trichophytide). Many of the papules develop a horny spine at the mouth of the follicle, producing the clinical lesion of lichen spinulosus, and, as **Jadassohn** pointed out, many cases described as lichen spinulosus are really cases of lichen trichophyticus. In 1905, **Lewandowsky** described a case of lichen spinulosus in a girl who had kerion on

the scalp. The lesions were those of lichen trichophyticus, but **Lewandowsky** did not recognise the connection between the eruption and the scalp kerion. Of course, it is not to be assumed that all cases of lichen spinulosus are due to ringworm, as the disease has been reported by **Adamson, Calcott Fox, Graham Little, Macleod, Audry, Halberstadter,** and many others in cases where no ringworm existed. But it throws light on the possible origin of these cases of lichen spinulosus, and suggests that in all cases the lesion is due to the reaction produced at the follicles by some toxin or organism coming either through the circulation or by external application into contact with a sensitised skin.

Guth examined the lichenoid lesions microscopically, and found the same histological changes as **Lewandowsky** described in his so-called lichen spinulosus, namely, a follicular inflammation with œdema, vacuolation of the epithelial cells of the outer root sheath of follicle, and a small-celled infiltration in the surrounding corium. In places the epithelium of the follicle is destroyed and a small intrafollicular pustule is formed surmounted by a mass of horny cells. The adjacent skin epithelium shows acanthosis. In the later stages the pustulation and signs of acute inflammation largely disappear, and the follicle shows a parakeratosis, which leads to the formation of the horny spine. This parakeratosis may be so marked as to prevent the hair getting out. The connective tissue around occasionally shows a mucoid degeneration, but the elastic tissue is never affected. In the eczematoid forms where the changes are not limited to the neighbourhood of the follicles, **Guth** found spongiosis of the epithelium, vesicle formation and parakeratosis with more or less acanthosis.

In all cases the cell infiltration in the corium consisted entirely of small round cells, with no sign of giant cells. A special form of the lichenoid trichophytide is the corymbiform trichophytide described by **Jadassohn** and **Saeves**. The latter's case was that of a man who was infected with cattle ringworm on the body. Around the larger deep-seated lesions were numerous smaller ones arranged in a corymbiform manner. The smaller lesions were bright red follicular nodules. In addition, on the body and limbs were numerous small red lesions of lichen trichophyticus. In the large central lesions fungus was found, but not in the small follicular ones. The large lesions had been present for 18 days

before the small lichenoid ones appeared. The latter also disappeared without treatment. These corymbiform lesions are similar to those seen in syphilis, in tubercle, and scrofuloderma lesions, and in leprosy (**Jadassohn**). **Saeves** discusses the pathogenesis of these corymbiform lesions. There are three possibilities :—

1. Blood spread.
2. Lymphatic spread.
3. External auto-inoculation.

As **Jadassohn** has shown in syphilis, the lymphatic spread is the most probable in that condition, the area immediately around the lesion being relatively immune. In the corymbiform trichophytide a similar explanation is possible, but there is still the possibility of an external spread. If trichophytin is rubbed into a sensitised skin a lesion exactly like lichen trichophyticus can be produced, and **Saeves** suggests that the patient whilst rubbing an ointment into a ringworm lesion may rub the fungus into the sensitised skin round about, and so produce the corymbiform appearance. **Saeves** considers that the lymphatic or external route is the probable one in the corymbiform cases, and that the generalised eruptions are probably produced by a blood spread.

Pedersen found that the skin around deep-seated ringworm lesions reacted more strongly to trichophytin than did the skin of more distant areas. One might argue that that supports the external origin of the corymbiform trichophytide, but **Pedersen** thinks that it does not necessarily support that theory, because if the reaction occurs through a blood infection the more sensitive area round the lesion would react more readily than other areas.

VESICULAR TRICHOPHYTIDES

Rasch describes 5 cases in which he saw eruptions generally consisting of vesicles or vesico-pustules the size of a pin's head. In another case he found a similar eruption in large groups on the buttocks, once on the arms, and once on the toes. This eruption was found twice on the scalp and adjacent parts of the forehead and temples.

It is a question whether these lesions should not be included under those to be next discussed, viz. the pustular trichophytides.

PUSTULAR TRICHOPHYTIDES

As already mentioned, some of the lesions in the lichenoid trichophytides may show pustulation, but **Bloch** described a case of extensive scalp kerion in a child who developed on the body and extremities a symmetrical rash consisting entirely of pustules on an inflammatory base. They were arranged sometimes in groups, at other times in large irregular patches, but the majority of lesions were isolated and some showed a follicular distribution. The contents of the pustules were sterile. The general condition of the child was gravely affected. There was shivering, rise of temperature, swelling of the lymphatic glands, and a leucocytosis in the blood. The intradermic trichophytin test was strongly positive on 3 occasions, and on each occasion the day after the injection there appeared round the seat of injection an erythemato-pustular eruption exactly similar to that on the body. For 15 days the child's general condition was alarming, and only improved as the kerion lesions began to subside. As the kerion became better, the pustular lesions gradually disappeared.

ECZEMATOID TRICHOPHYTIDES

Eczematoid trichophytides have been described by **Jadassohn** and others. They are really a sub-variety of the lichenoid form in which the lesions are so closely set together that they form scaly patches not unlike a seborrhœic dermatitis. **Guth** also describes 1 case of kerion, which showed a rash on the body resembling pityriasis rosea.

SCARLATINIFORM TRICHOPHYTIDES

Sutter describes a case of a girl of 10 years of age with a kerion of scalp due to Trichophyton granulosum. On the 15th day of the disease, and 5 days after the head had been X-rayed, the child suddenly complained of headache and vomited. A scarlatiniform rash appeared all over the body and limbs. The exanthem consisted of a punctate erythema beginning in small patches, which rapidly coalesced and resembled scarlet fever very closely. The mucous membrane of the palate, pharynx, and gums showed a diffuse redness. The conjunctivæ were slightly

reddened. The temperature rose and remained up for 8 days. There was marked swelling and tenderness of the cervical, supra- and infra-clavicular, and axillary glands. The right retro-auricular and cervical glands were swollen and fluctuating. On puncture of these glands, pus was obtained, and although no fungus was seen microscopically, cultures from the gland contents gave a pure growth of trichophyton granulosum, the same as had been obtained from the kerion scalp lesions. The spleen also was enlarged, and the blood showed a polymorphonuclear leucocytosis of 16,800 per ccm. The diazo reaction was positive. The child also complained of pain and swelling of the joints, especially of the right foot and left knee. The joints were painful on movement and showed an increase of fluid in them.

As the temperature fell the rash altered in character. It became more papular and papulo-pustular and follicular, and in places annular or eczematoid like the cases of lichenoid trichophytides already described. In the subcutaneous tissues of the legs there appeared several swellings, tender to pressure and resembling erythema nodosum (see Nodular Trichophytides later).

At this stage the softened retro-auricular gland was excised and found to show a necrobiosis in the centre with masses of leucocytes all round, among which were numerous mycelial threads. Several giant cells were also visible.

The trichophytin intradermic test and the Moro test with 20 per cent. trichophytin ointment were both positive. Four papules were excised from the exanthem, and from these cultures of the trichophyton granulosum were also obtained. Therefore in this case the same fungus as caused the kerion was found in the skin rashes and lymphatic glands. The fungus was obtained culturally from the surface of lichenoid lesions 48 hours after their appearance, but not later on either in the scales or crusts from the lesions.

Sutter also describes 2 analogous cases, 1 with a kerion of scalp in whom a rash like that of scarlet fever appeared on the body and mucous membranes, but without swelling of glands or spleen. This rash later became papular and spinulous. The other was a kerion case, in whom an injection of 0·1 c.c. trichophytin subcutaneously resulted in a rigor with a rise of temperature and a macular rash on the chest, abdomen, and mucous

membranes. This rash was exactly analogous to those sometimes produced in tuberculous cases by the injection of old tuberculin.

NODULAR TRICHOPHYTIDES

(*Erythema nodosum trichophyticum*)

This form of trichophytide was first described by **Bloch** in a case with an extensive kerion, together with a very marked lichen trichophyticus on the body and arms associated with fever, leucocytosis, enlargement of lymphatic glands and spleen. Then rather suddenly on the extensor aspect of the legs there appeared numerous cutaneous and subcutaneous nodules, of firm consistence, tender on pressure, and of a reddish or bluish colour. Clinically the lesions were indistinguishable from an ordinary erythema nodosum. After injection of trichophytin a very definite focal reaction occurred in the nodules. One of the nodes in excision showed an inflammatory infiltration of the derma and hypoderma.

Since this case was published, **Bloch** has recorded another case, and cases have been reported by **Sutter, Pulvermacher, Guth,** and **Bruusgaard.** In all 8 cases have been published. All cases occurred in the course of a severe infection with ringworm associated with general symptoms. All except 1 case (which occurred in a tinea barbæ) were in children with kerion. With the exception of **Pulvermacher's** case, in which the arms and buttocks were involved, the nodules were situated on the lower extremities and usually on the anterior aspect. The eruption came out suddenly and lasted for weeks. Both **Bloch's** cases gave a positive focal reaction on injection of trichophytin. The view that the lesion probably starts from a vein was supported by one of **Pulvermacher's** cases in which there was a hard string of nodules in the course of the great saphenous vein. The question naturally arises as to whether these cases are to be regarded as nodular trichophytides or as cases of kerion with erythema nodosum in addition. The fact that they showed lichen trichophyticus as well is a point in favour of their being trichophytides. A positive focal reaction on injection of trichophytin is also in favour of the same view. The question has already been referred to under Erythema Nodosum (p. 69).

But the final proof of their trichophytic origin was given recently by **Bruusgaard,** who excised one of the nodules in his case. He selected a fresh nodule scarcely 24 hours old. Histologically the lesion showed a marked inflammation with numerous polymorphonuclear leucocytes in the pars reticularis of the corium with œdema and proliferation of the connective tissue cells. The papillary blood-vessels were very congested, and hæmorrhages had taken place. Among the cell infiltration of the corium numerous deeply-stained spore-like elements were seen, either isolated or in groups. From the node also a pure culture of the trichophyton gypseum was obtained—the same fungus which had previously been grown from the original tinea barbæ lesion in this case.

ERYTHEMA MULTIFORME TRICHOPHYTICUM

Two cases of this condition have been described by **Bloch.** The one was a female patient with chronic gonorrhœa who was inoculated on the left arm with Achorion Quinckeanum, and soon developed a vesicular and scaly spreading lesion of the size of a florin. After an intradermic injection of trichophytin (0·1 grm.) a very marked local reaction was produced at the seat of injection. This inflamed area spread during the following days, producing a large swollen area with raised edge over the greater part of the arm. Three days later an eruption appeared on the backs of both hands in the form of flat, rounded erythematous areas. These enlarged, spread to the backs of fingers and palms, elbows, and face, and showed the usual rounded lesions of erythema multiforme with bluish centre and red edge. This eruption took about 6 days to spread and then gradually disappeared.

Bloch also refers to, but gives no details of, another analogous but less extensive case.

Although **Bloch** claims these as trichophytides of erythema multiforme type, in the first case at least it seems to me there might be some doubt as to the correctness of that opinion. The marked swelling at the seat of injection and its spread to the greater part of the arm, like a lymphangitis, suggests that the area of injection might have become infected with some septic process, and from that the multiforme rash might have proceeded.

Rasch also describes a case of a deep-seated tinea barbæ which showed on the backs of the hands, lower arms, and knees an eruption of erythematous lesions with a small vesicle in the centre of each. **Rasch** considered it typical of erythema multiforme.

MICROSPORIDES (Lichen Microsporicus)

In addition to the trichophytides in infections with large-spore ringworm, similar lesions have been described in association with small-spore infections, but the reports are much less numerous than in large-spore cases. The first report of such a case was made in 1917 by **Chable** in a child aged 3½ years who had a typical kerion from which Microsporon Audouini was cultivated. Five days after the kerion developed, the child complained of pains in the joints and vomited. The temperature rose to 38·4° C., and next day almost all the body was covered with a small papular eruption (lichen microsporicus). The limbs were slightly affected. This eruption remained for about 3 weeks, gradually fading and becoming brownish in colour. Some of the papules showed some hyperkeratosis at the mouths of the follicles, but some became definitely spinulous. An intracutaneous injection of trichophytin, a few days after the rash appeared, produced a marked local reaction at the seat of injection. The scalp lesion in this case began as an ordinary small-spore tinea and developed into a kerion after the head had been X-rayed, when the hair was partially out after the raying.

In 1921 **Arzt** and **Fuhs** published reports of cases of lichen trichophyticus, together with 1 case of ordinary small-spored tinea capitis, due to Microsporon Audouini which showed a lichenoid rash.

In 1922 **Arzt**, in an epidemic of 250 cases of small-spore ringworm, saw exanthemata on the body in 12 of them. Two of the cases showed an ordinary scaly tinea capitis with no signs of inflammation. Five showed slight inflammation with red scaly areas, and 5 showed marked inflammation with pustulation and crusting, but without any definite kerion lesions. Clinically, the exanthem was not quite the same in all cases. Usually the body or body and limbs were affected, and occasionally the face.

In most cases the rash was lichenoid in character, but small vesicular lesions going on to pustules and eczematoid lesions were also seen. In 2 cases the lymphatic glands were enlarged. All 12 cases had been X-rayed, and the rash came out after that and usually in from 2 to 3 weeks after raying. In all cases trichophytin (he had no microsporin) in doses of 0·1–0·3 was injected intracutaneously. Five cases showed an exanthem 24 hours later, and in 5 cases a rise of temperature was seen. **Arzt** also succeeded in finding the fungus in scales and by culture from the lichenoid lesions. In excised lichenoid lesions he did not succeed in finding the fungus microscopically. Blood cultures were also made, but were negative.

From the above it is evident that in small-spore tinea capitis, even in cases not differing from the ordinary scaly variety, general exanthemata may occur similar to the trichophytides.

FAVIDES

Eight cases of favides similar to trichophytides and microsporides have recently been recorded by Italian observers. **Martinotti** reports 3 cases, all occurring in patients with favus capitis due to Achorion Schönleinii. All were of the small papular type and indistinguishable from trichophytides. In 2 of the cases the eruption appeared after X-ray applications for treatment. **Ambrosoli** reports 1 case of favus capitis due to Achorion Schönleinii in which, 6 days after the head was X-rayed, a papulo-squamous eruption appeared suddenly on the trunk and proximal parts of upper and lower extremities. There was a slight rise of temperature, a lymphocytosis in the blood, and swelling of all the lymphatic glands. The achorion was demonstrated both microscopically and culturally in the eruption on the first day or two after its appearance.

PERSONAL EXPERIENCES OF TRICHOPHYTIDES AND MICROSPORIDES

During the last year or two I have been on the look-out for generalised rashes in cases of ringworm of the scalp. In hospital practice, where very large numbers of cases are to be examined,

it is hardly feasible to examine the whole body in every case of ringworm of the scalp, but all the inflamed ringworms have been stripped and examined. There are 2 types of inflamed cases seen in Edinburgh. First, the true kerion, which, although sometimes due to a trichophyton, is quite frequently due to the Microsporon Audouini, and, secondly, a more widely distributed inflamed condition of the scalp with superficial pustulation. In only a few cases has any rash been noticed, so that the condition cannot be at all frequent.

Case 1.—This was seen in the early stage and was one which occurred in the private practice of **Sir Norman Walker**, who kindly allowed me to see it. The child was a boy of 10 years of age, the son of a farmer. He had suffered from a deep-seated ringworm on the nape of the neck for 6 weeks. There were no other affected children, but 1 of the bullocks on the farm suffered from ringworm. In 3 weeks after the first skin lesion appeared other diseased areas occurred in the neighbourhood, and a week before the boy was seen numerous spots appeared on the body. The lesions on the back of the neck were swollen, pustular, and resembled kerions, and in them hairs containing large-spore fungus were found. The rash, which came out suddenly, was distributed more or less all over the body, and consisted of lichenoid papules, some of which showed a necrotic centre covered with a crust. Some of the lesions were larger and might be described as nodules. On the sides of the body they were so closely set together as to form patches like seborrhœides or an early psoriasis. They resembled very closely the rash of lichen scrofulosorum, and I think there is no doubt that this was an example of a papulo-necrotic trichophytide. The boy's general condition was apparently unaffected.

Case 2.—A boy aged 7 years showed on the scalp red scaly areas which were almost bald when first seen. The father said that the areas had been swollen, red, and tender when they first appeared. They were obviously areas of healing kerion. No fungus was to be found now in the lesions. On the back and both sides of the chest, especially the right side, were several oval areas very slightly red and covered with small spines which projected from the follicles. The father had not noticed these before, but I think they must be considered as the later stage of

the lichenoid and eczematoid trichophytide which had gone on to the spinulous stage. They resembled scaly seborrhœides except for the marked horny spines. Had the child been seen earlier he would probably have shown the lichenoid stage of the lesions.

Case 3.—A boy $7\frac{1}{2}$ years of age was seen in private with a kerion which had lasted for 4 weeks. The kerion lesions were numerous but less inflamed than they had been. His mother said that a fortnight before I saw him the child suddenly developed a rash all over the body and legs. For some days the child was feverish and out of sorts. When I saw him, this rash had completely disappeared from the body, but the lower limbs still showed several scaly red areas resembling seborrhœides. I think this case also may be considered as an eczematoid trichophytide, which was disappearing.

Case 4.—A boy aged 3 years showed a kerion on the top of the head with numerous pustular lesions on the rest of the scalp. After this had lasted for 2 weeks he suddenly developed a small red scarlatiniform rash all over the chest, abdomen, and proximal parts of limbs. It remained out for 3 or 4 days and then faded. The child had no sore throat nor temperature and the face was not affected. The tongue also was normal. The rash did not develop into lichenoid lesions as **Sutter's** case did, so that it is doubtful whether this case was a scarlatiniform trichophytide or a septic rash due to absorption from the pustular lesions on the scalp.

Case 5.—A girl aged 11 years developed kerion lesions on the scalp 16 days after being X-rayed for a scaly tinea capitis due to infection with small-spore ringworm from a cat. A few days later she showed numerous scaly red papules on the neck, body, and arms. These persisted for about 10 days and gradually became browner in colour and faded. There was no disturbance of the general condition. No fungus could be found in the papular regions. I think they are to be regarded as microsporides and, as they were much more numerous on the neck, shoulders, and upper chest than elsewhere, it suggested that they were due to an exogenous spread from the infected hairs which had fallen out after the raying and had been rubbed into the skin.

Case 6.—I have to thank **Dr F. Gardiner** for kindly allowing me

SMALL PAPULAR TRICHOPHYTIDE.

to record this case. The patient was a boy aged 5 years who showed 1 very large typical round kerion lesion near the crown of the head with a smaller one on the left side of head. The kerions had been present about 3 weeks. On examination, the neck, trunk, upper parts of upper and lower extremities were found to be covered with a papular eruption. The papules were pale bluish pink with a brown tinge in places. They were arranged follicularly and fairly evenly distributed over the skin surface, but with a tendency to grouping. Most of the lesions had a small scale at the apex, but quite a number showed a definite horny spine projecting from the mouth of the follicle. They were not itchy. The glands at the back of neck, axillæ, and groin were slightly enlarged. The father, who came with the child, said the eruption had not been noticed, but, on being questioned, said the boy did not seem to be very well and was off his food about a week previously.

There is no doubt the above case was a typical example of a lichenoid trichophytide. The accompanying Plate shows the appearance of the lesions on the right shoulder region.

There are two other points which I have noticed with regard to trichophytides and to which I should like to refer.

Firstly, in a considerable number of cases of kerion when the body was examined here and there, especially on the sides of the chest, isolated spiny projections were seen sticking out of the follicles. There was no history of any rash being noticed in these cases, but it is possible that a rash might have occurred and passed unnoticed, and that these spinulous lesions were the only visible remains of it.

Secondly, a very considerable number of cases of ordinary scaly ringworm of the scalp, mostly due to the small-spore fungus, develop an extensive pustular eruption all over the scalp about a fortnight or so after exposure to X-rays. The pustules are rounded and slightly flattened on the top and have a very red inflamed base and are always associated with enlarged tender glands in the occipital region. The pustulation persists long after the hair has completely fallen out. When it first begins the lesions are very tender and the child often looks out of condition. No fungus has ever been found in the pus. Are these lesions due to a secondary infection with a septic organism or are they

trichophytides or microsporides ? As they remain more or less localised to the scalp and do not spread except to the adjacent forehead, temples, and neck, it suggests that they are septic in origin. These cases also seem to occur in epidemic form, especially in the children who are attending the special ringworm school, suggesting an infection which spreads from case to case. On the other hand, the lesions look extraordinarily like the vesico-pustular trichophytides figured on the scalp by **Rasch.** The fact that they nearly always arise just as the hair is beginning to come out after X-rays is also significant. They might be due to the loose hairs containing fungus getting rubbed into the scalp in the process of rubbing in the ointment used in treatment, and if the child is sensitised to the infection, in that case a vesico-pustular or pustular reaction would take place. This reaction would not take place in a non-sensitised case.

PATHOGENESIS OF TRICHOPHYTIDES, MICROSPORIDES, AND FAVIDES

In the first place, it would be well to satisfy ourselves that these various eruptions described are really trichophytides and directly associated with the ringworm infection. That being determined, it has to be shown how they arise.

The fact that they always occur in cases of ringworm, and usually in deep-seated suppurating cases, would at once suggest the connection. Then all these cases show a well-marked allergic condition of the skin, as is shown by the presence of a positive cutaneous or intracutaneous trichophytin reaction, as shown by **Guth, Saeves,** and others. This, as one would expect, is essential to the production of trichophytides. **Pedersen** showed by trichophytin skin tests that this hypersensitiveness of the skin was specially marked in the skin round the lesions and on the arms where trichophytides usually occur, and **Sutter** confirmed this, using the living fungus instead of trichophytin. **Jadassohn** and **Bloch,** by rubbing in trichophytin ointment into the skin in these cases, produced a lesion indistinguishable from lichen trichophyticus. The fact also that fungus has been seen microscopically and grown from the lichenoid lesions and enlarged glands further proves that it is the causal agent. Therefore, I think, there is no

doubt that the various lesions described as trichophytides are the result of the ringworm infection.

Let us now consider how they are produced. There are three possibilities:

1. Lymphatic spread.
2. Exogenous spread.
3. Hæmatogenous spread.

1. *Lymphatic Spread.*—This naturally could only be possible in localised trichophytides, and could never explain the wide-spread lesions found in most cases, but, as already indicated, that might be the means of spread in the corymbiform trichophytide.

2. *Exogenous Spread.*—This method is suggested by the fact that lesions identical with lichenoid trichophytides can be produced by rubbing trichophytin into the skin of patients allergic to ringworm. **Du Bois** examined the skin of patients suffering from scalp ringworm and found that from practically any part of the apparently healthy skin surface the fungus can be obtained. The clothes rubbing on the skin might rub such fungus into the follicles and so produce the follicular lichenoid lesions. That, however, is rather unlikely to occur all over the body at once, as the trichophytides usually develop suddenly and simultaneously all over. It might, however, and doubtless does account for some of the less extensive trichophytides and especially those that occur on skin areas near the ringworm focus. This would explain especially those cases where the lesions occur on the neck and shoulders where broken hairs containing fungus are likely to fall down and become rubbed into the skin.

3. *Hæmatogenous Spread.*—A spread through the blood stream is the one which naturally suggests itself as the most likely one. The eruption comes out suddenly and has a symmetrical distribution. The resemblance of the lichenoid and scaly forms to lichen scrofulosorum, and of the nodular forms to erythema induratum, both of which are generally allowed to be hæmatogenous in origin, support this view too. The presence of fever, headache, joint pains, a blood leucocytosis, with a general enlargement of the lymphatic glands throughout the body and of the spleen, and a positive diazo reaction, all point to a general infection. The finding of the fungus in the lesions by **Guth** and

Sutter also shows that in some, if not all cases, it is present. The fact that some workers did not find fungus is of no great importance. Analogous negative results were sometimes obtained in tuberculides, yet that does not in any way detract from the value of other positive findings.

The time at which the lesion is excised is probably also important. It is only in cases where the lesion is excised within 48 hours or so of its appearance that one would expect to find the fungus, as the reactionary processes going on in the skin are designed to destroy and eliminate the fungus. The finding of fungus in the cervical and retro-auricular glands does not necessarily prove that it got there through the blood stream, as it might have spread from the scalp by the lymphatics. It is a valuable contribution to our knowledge, however, as that may be the route by which the fungus reaches the circulation eventually. It might spread, as the spirochæte in syphilis does, from the primary lesion by the lymphatics to the nearest glands, and from there get into the circulation. **Saeves,** by injecting intracardially an emulsion of ringworm spores, succeeded in producing foci in the skin from which the fungus was recovered. The most important advance, however, in these investigations was made in 1921 by **Ambrosoli.** The case was a kerion in a child aged 11 years. From the kerion lesion the Trichophyton gypseum asteroides was cultivated. After 5 or 6 days in hospital the child developed a temperature of 38·5° C., and on the sides of the neck small follicular papules appeared. These were bright red in colour at first and showed small vesicles. During the next 2 days the rash spread to the thorax, abdomen, and outer aspects of upper extremities. Repeated examination of scales, etc., from the surface of these lesions were negative. The inguinal and cervical glands and the spleen were slightly enlarged. The blood showed an increase of the polymorphonuclear leucocytes. Therefore he was dealing with a typical case of trichophytide.

Whilst the rash was at its height blood cultures were made. Several cc.'s were withdrawn from the median cephalic vein with antiseptic precautions and put on **Sabouraud's** maltose medium in 4 tubes, 2–3 cc. into each. Cultures were similarly made again next day from blood similarly withdrawn and 4 tubes were again inoculated. The first set of cultures were

negative, but in the second set, after 8 days, a typical culture of Trichophyton gypseum asteroides grew. This, therefore, definitely proves that in trichophytides the fungus is actually circulating in the blood stream.

This observation of **Ambrosoli** was confirmed in the same year by **Jessner.** His case was that of a boy aged 10 years who suffered from the ordinary superficial tinea capitis. This boy suddenly developed a lichenoid trichophytide with some eczematoid lesions all over the body, face, and neck. The cervical glands were enlarged, and puncture of one of the enlarged glands was negative as regards fungus both microscopically and culturally. The blood showed a polymorphonuclear leucocytosis of 16,000 per ccm. There were no mucous membrane lesions and no fever. Slight bronchitis was present in both lungs. Five days after the eruption appeared blood cultures were taken. Twenty cc. of blood were withdrawn from a vein and plated on maltose and glucose agar. In these a culture grew exactly the same as the one obtained from the scalp hairs. This culture was a little difficult to identify. At first it looked like Trichophyton granulosum, but later **Jessner** was more doubtful. **Plaut,** who saw it, said it belonged to a kind of botrytis, which grows as a saprophyte on dead plants and vegetation and belongs morphologically to the trichophytons. Inoculated into 2 guinea-pigs, 2 adults, and 2 children, the results were negative, but when inoculated on a colleague who was allergic after an attack of deep-seated ringworm, it gave a positive reaction. This fungus also, when inoculated on the skin of a female colleague, produced a superficial erythemato-squameous ringworm from which the fungus was again obtained by retroculture.

Jessner also describes a second case in a boy of 11 years of age with a kerion. He could not get a pure culture from the kerion. The cultures were all spoilt by contaminations. This child developed a lichenoid trichophytide on the body with a leucocytosis of 28,000 per ccm. The trichophytin skin reaction was positive. Blood cultures showed 1 colony of Trichophyton gypseum which on inoculation on 2 men produced typical superficial tinea corporis. Therefore, from these observations, there can be no doubt that if cultures are taken early enough the fungus can be obtained from the circulating blood.

Comparing the different routes by which trichophytides may arise, we may conclude, therefore, that in the majority of cases, especially the generalised ones, the spread is by the hæmatogenous route, but in less extensive ones near the lesion the spread may be externally, or in some cases as in the corymbiform lesions by the lymphatics.

Although we have seen that the lesions produced by hæmatogenous spread are due to the fungus itself circulating in the blood, some of the trichophytides may not be produced by the fungus elements circulating in the blood and sticking in the skin capillaries of the allergic skin and there producing a reaction which is seen as the trichophytide. They may be due to the skin cell becoming sensitised to the fungus infection and the toxins of the fungus absorbed from the kerion lesions producing a reaction when circulating in the allergic skin. This is especially suggested in the scarlatiniform trichophytide which looks so extraordinarily like the rash sometimes seen on injection of old tuberculin in tuberculous cases. In such cases the rash may be due to the lighting up of a previous trichophytide. **Bloch** thinks that the fungus emboli do not act as parasites in the tissues, but that the endo-toxins which they contain, and which are set free by the rapid lysis of the spores and mycelium in the skin, produce the lesions. **Bloch** had a case of kerion of the scalp in a boy, aged 16 years, with numerous superficial foci of ringworm on the face and arms. In addition, he had fever, swelling of the cervical glands, blood leucocytosis, and on the body a lichenoid trichophytide. The trichophytin skin reaction was strongly positive. After complete disappearance of all symptoms, **Bloch** began giving the patient intravenous injections of trichophytin. He received in all 3 cc. pure trichophytin in 20 days. There appeared at first a scarlatiniform erythema, and later, on the trunk and limbs, a typical lichenoid trichophytide.

In another case which had a pustular trichophytide after its complete disappearance, subsequent intravenous injections of trichophytin produced a typical lichenoid trichophytide.

Thus it is possible that some trichophytides, especially the scarlatiniform and small lichenoid ones, may be due to the toxins of the fungus.

From this general survey of the whole subject of ringworm

and allied fungus infections, it is evident that these infections are not, as used to be supposed, purely local ones. In a great many cases the infection has great analogies with what occurs in infections like tubercle, syphilis, etc. When sensitisation occurs, the whole reactive mechanism of the body is brought into play with the production of a marked skin hypersensitiveness, which leads to the production of the various skin reactions and rashes which have been described.

SUMMARY

1. Ringworm, especially the deep-seated varieties, produces general as well as local effects.

2. Injection of an extract of ringworm fungus (trichophytin) in cases of deep-seated ringworm in human beings leads to a local reaction at the seat of injection, a focal reaction in the lesion, with a general reaction with rise of temperature and signs of intoxication.

3. These reactions are not, as a rule, present in cases of superficial ringworm.

4. Animals such as the guinea-pig and rabbit can be readily infected with certain kinds of fungus, especially Trichophyton gypseum and Achorion Quinckeanum.

5. The lesions in animals heal spontaneously, leaving behind a sensitiveness of the skin as evidenced by a positive cutireaction and a lasting immunity.

6. Neither the sensitisation nor immunity is specific for the fungus employed.

7. Immunity is only produced by skin inoculation. Intraperitoneal and subcutaneous inoculation do not produce the same result.

8. Immunity is only produced by an actual infection. Injection of trichophytin or favin does not cause immunity.

9. The immunity is not in all cases absolute, but may be only relative.

10. In animal experiments a second infection with ringworm always runs a modified course from the first infection, usually with a shortened incubation period and more rapid course. The lesion produced on a second inoculation is to be considered as a hypersensitive reaction rather than as a true reinfection.

11. Immunity produced by infection in animals can be inherited both when the mother's immunity is acquired before conception and during the pregnancy.

12. There is no evidence of any local immunity of the skin in areas which have been affected with ringworm.

13. Active immunity to ringworm and favus has been produced by some workers by injection of trichophytin and by rubbing dead fungus extracts into the skin. The immunity produced is only a partial one.

14. Attempts to produce passive immunity to ringworm were unsuccessful.

15. In deep-seated ringworm the blood shows a polymorphonuclear leucocytosis. The same change also occurs in the blood in ringworm cases and immune persons after injection of trichophytin. Healthy persons injected with trichophytin show a lymphocytosis in the blood. A similar lymphocytosis was found in superficial, small-spore tinea capitis and in favus capitis.

16. In deep-seated ringworms, and to some extent in superficial ringworms and in favus, precipitins, agglutinins, and complement-fixing bodies are present in the serum. All these reactions were found not to be specific for the fungus causing the disease, but to occur more or less markedly with all fungus antigens.

17. Cases of ringworm, especially the deep-seated varieties, give a positive cutaneous and intracutaneous reaction to fungus extracts (trichophytin). This reaction may still be present as long as 29 years after an attack of ringworm. Some observers found the reaction, especially the intradermal one, to be nonspecific, as it occurred in normal individuals and persons suffering from other chronic diseases. The intracutaneous reaction was also found to be quantitatively rather than qualitatively specific. In young infants the reaction was absent. It was also absent in the exanthemata and cachexia. This corresponds with the absence of the tuberculin skin tests in these conditions.

The trichophytin skin reaction is more marked on areas such as the abdomen, where the trichophytides occur, and in the skin round ringworm lesions than elsewhere. Repetition of the test causes a gradual decrease in the severity of the reaction.

18. In the majority of cases of favus, cutireactions to trichophytin and favin were absent.

19. The author tested 11 cases of small-spore tinea capitis, 7 of large-spore ringworm, and 8 of favus. The method used was the cutaneous Pirquet method. In each case extracts of the same fungus which caused the disease were used.

Extracts A (containing toxins in fluid medium before fungus crushed);

Extracts B (containing toxins in fluid medium after crushing of fungus);

Extracts C (containing masses of crushed fungus)

were used. The A extracts in no case produced a positive reaction. The B and C extracts in practically all cases gave similar results. Doubtful reactions were considered negative.

With B and C extracts in small-spore tinea capitis 1 case out of 11 gave a positive reaction, *i.e.* in about 9 per cent.

In 8 cases of favus 1 reacted positively, *i.e.* 12·5 per cent. All the large-spore cases were negative.

20. A transplantation experiment by **Bloch** demonstrated the fact that the skin cell itself is sensitised after an attack of deep-seated ringworm.

21. In certain cases the fungus of ringworm and favus may produce large cutaneous and subcutaneous granulomatous masses consisting of round cells, epithelioid cells, and giant cells (granuloma trichophyticum (**Majocchi**) and granuloma favicum). These granulomata differ from kerion and the "lumpy" lesions of tinea barbæ in that actual ulceration takes place.

22. Cases of ringworm can be cured without local treatment by injections of trichophytin. Intradermic injection was usually found to be more efficacious than subcutaneous injection. Rubbing in a trichophytin ointment was also successful in some cases. Extracts of the actual fungi were much more potent than culture filtrates. Good results were obtained in both superficial and deep tineas and in favus, but especially in deep lesions. Certain trichophytins, such as the one prepared from Achorion Quinckeanum, gave much better results than others.

23. Encouraging results were also obtained by **Loeb** in the treatment of deep and superficial tineas with a staphylococcal vaccine.

24. The author obtained disappointing results in the treatment of a few cases of small-spore tinea capitis with microsporin. **Strickler,** however, claims to have cured similar cases by this method.

25. Generalised rashes may occur in cases of ringworm both superficial and deep seated, especially the latter, and in favus. These are known as trichophytides, microsporides, and favides. They may be papular (lichenoid trichophytide or lichen trichophyticus), with or without horny spines (lichen spinulosus), vesicular, vesico-pustular, pustular, eczematoid, scarlatiniform, erythematous (erythema multiforme trichophyticum), or nodular (erythema nodosum trichophyticum). A more localised corymbiform trichophytide may also occur.

26. These trichophytides, microsporides, and favides are due in the widespread cases to a hæmatogenous spread of the fungus, but in the less extensive cases the spread may be exogenous and in the corymbiform lesions may be lymphatic. In all cases an allergic condition of the skin is essential.

SENSITISATION AND IMMUNITY TO SPOROTRICHOSIS AND OTHER FUNGUS DISEASES

Sporotrichosis resembles ringworm in that it is due to a fungus—the sporotrichum—which produces lesions in the skin very similar to the granuloma trichophyticum already described. It differs, however, in being a more widespread infection and in affecting internal organs as well as the skin. Only 1 case of this disease has been described in Scotland, and that was a case reported in 1911 by the late **Professor James Ritchie** and **Sir Norman Walker.** This case was typical of the local inoculation of the fungus, producing a primary lesion on the finger from which a spread took place up the arm by the lymphatics, leading to the formation of numerous indolent swellings which suppurated and ulcerated. Besides this localised form numerous cases have been described, especially in France, where a generalised infection took place either following the local infection or without any previous visible point of inoculation. Multiple gummatous lesions may occur on the skin, mucous membranes, bones, muscles, joints, eyes, and internal organs, such as lungs, etc.

As would be expected, cases of sporotrichosis show marked general reactions in the tissues. **Widal** and **Abrami,** and **Beurmann** and **Gougerot** have shown that the serum gives positive complement-fixation reactions, using the fungus as antigen. Positive agglutination reactions are also present. **Widal, Sicard,** and **Gougerot** showed the presence of precipitins in the serum, and **Milhit** the presence of opsonins. Indicating that the patient is allergic in sporotrichosis, intracutaneous and subcutaneous injection of dead fungus also leads to positive reactions. But all these reactions are not specific. The presence of any other fungus infection will cause these reactions to occur. **Beurmann** and **Gougerot** also showed that an active immunity can be produced to sporotrichosis in animals by inoculation of dead or living cultures of the fungus. An anti-sporothrix serum can also be produced which has both immunising and curative properties.

The changes in the blood serum and tissues generally are much the same as can be produced by some ringworm fungi, but there is this difference, that no general rashes resembling the trichophytides have ever been described. Why this should be is rather curious, as the cutireaction is present in these cases one would expect " sporotrichides " to occur. Of course the multiple gummatous lesions which occur in general infections with sporotrichosis might be looked upon as analogous to the nodular trichophytides, but they do not show the same tendency to spontaneous healing which the latter do. They are exactly similar to the lesions in granuloma trichophyticum, which also, as in **Sequeira's** case, do not tend to heal spontaneously. It is possible that in sporotrichosis and in granuloma trichophyticum there is too much fungus present in the lesions or it is too active in its growth to allow of the tissues destroying it easily.

Sporotrichosis, although it leads to a sensitisation of the tissues, as evidenced by the cutaneous and blood-serum reactions, does not confer a good immunity. The patient never seems to get beyond the sensitised stage.

In Blastomycosis of the skin, **Gilchrist** found that the serum of the patient gave a positive agglutination and a positive complement-fixation test with the parasite obtained from the lesions. These reactions, as in sporotrichosis, are not specific, but may be

useful to distinguish the lesion from others not due to a fungus. So far as I can find, no cutaneous tests have been done in blastomycetes. Where a general infection has taken place and been treated, the disappearance of the complement-fixation reaction may be useful in determining whether cure has taken place in the internal lesions or not. This also applies equally well to sporotrichosis and other general fungus infections.

In Actinomycosis the researches of **Widal** and **Abrami** have shown the value of the complement-fixation and agglutination tests in such cases. **Abrami, Brissaud,** and **Joltrain** have also shown that an anti-actinomycotic serum which has a therapeutic value can be obtained. In this condition also I have been unable to find any report of cutaneous tests having been made.

Hemisporosis is a fungus infection due to the hemispora stellata which may produce cutaneous gummatous lesions as reported by **Gougerot** and **Caraven** and **Auvray.** Like all the other fungus diseases, general infections, especially of the bones, may occur. **Gougerot** and **Caraven** also found that the blood serum gives positive agglutination and complement-fixation tests with the fungus. As in all the fungus infections already described, these reactions are not specific, but their presence in hemisporosis indicates that the fungus, if found in the lesion, is the cause of the condition and not an accidental contamination.

In all those fungus infections, therefore, there are evidences of sensitisation as shown by cutaneous and blood-serum reactions. Although not specific, these reactions may be of assistance in diagnosis. An attack of one of these diseases does not produce any marked immunity. The production of active immunity and the curative effect of antisera indicate that there is possibility of a considerable degree of immunity being produced, but the body never seems to go beyond a stage of hypersensitiveness. In this respect they resemble closely the other granulomatous diseases such as syphilis, in which the hypersensitive condition leads to a marked reaction on the part of the tissues, but not of sufficient intensity to cause a complete destruction of the invading virus.

PRIMULA OBCONICA.

CHAPTER X

DERMATITIS VENENATA

Under dermatitis venenata are included all the forms of dermatitis due to external irritants. This form of dermatitis only affects certain individuals. A chemical substance or plant, which causes a dermatitis in one individual, may be handled by another individual with impunity. This special susceptibility of certain individuals to certain substances used to be put down to an "idiosyncrasy" on the part of the individual. It will be shown that this idiosyncrasy is really a sensitisation of the skin. It explains why one person is affected by a substance which has no effect on another, and why a man may work, for example, as a joiner for many years and quite suddenly suffer from a dermatitis every time he handles certain forms of wood, such as teak. I do not propose to describe the appearances of the eruption as these are well known, but will confine myself to the mechanism of the production of the sensitiveness, the nature of the substances involved, whether it is local or general, and whether desensitisation or immunity can be produced. Before discussing these questions I will describe a series of experiments which I did on myself and others to see whether individuals could be artificially sensitised. I used the *Primula obconica* (Plate opposite), because it is one of the plants which most frequently causes a dermatitis venenata.

Before starting to experiment with myself I could handle the primula and rub the leaf on my skin with impunity. I scraped the skin of the back of the left forearm with a scalpel over a small area of about 1 inch by $\frac{1}{2}$ inch till a moist oozing surface was produced. Into this area the crushed leaf of *P. obconica* was vigorously rubbed and the juice allowed to dry on. About 12 hours later the part was thoroughly washed

with soap and water. The area crusted over and healed completely in about 2 weeks, leaving a very superficial scar. At no time was there any itching nor inflammatory reaction beyond what is normal in a traumatic lesion.

Three weeks after this inoculation the unbroken skin of the same area on the left arm was again rubbed with the crushed leaf of the same primula and the juice allowed to dry on. This was done at 8 p.m., and on going to bed at 11 p.m. there was no change on the skin. I was wakened at about 4 a.m. with intense itching of the arm, and the skin of the rubbed area was red and slightly swollen. Next morning the whole rubbed area was redder, more œdematous, and still very itchy. The centre showed numerous minute vesicles with a wide erythematous area around. This erythema gradually spread up and down the arm. The Plate opposite shows the reaction at the end of 6 days. At the end of 10 days it was at its maximum, after which it gradually subsided.

About the 6th day the dermatitis showed a central very inflamed area, then a ring of less inflamed skin with a further more inflamed area outside that. This type of reaction did not occur so markedly every time I rubbed on the primula, but it has occurred more than once. It is probably due to the same cause as is suggested to explain the corymbiform arrangement of the rash in some cases of syphilis, viz. that there is an area of antianaphylaxis or antisensitisation round the central zone.

The itching was very marked and came on at intervals, usually being worst in the forenoons, evenings, and when I became warm in bed at night. If the area was rubbed (and one couldn't help doing so) the lesions flared up and became very red again. It was only after 28 days that the skin went completely back to normal.

Later, the skin of the other forearm and of the thigh was rubbed with the leaf of *P. obconica* with the same result, except that the reaction was slightly less intense and did not last quite so long (only 20 days). The right forearm was rubbed before the reaction on the left arm had completely subsided, and within 24 hours after rubbing the right arm the original area on the left arm became distinctly redder and itchier for a day or two than it had been, *i.e.* a focal reaction had occurred. This focal

Reaction to Primula Obconica on Author's

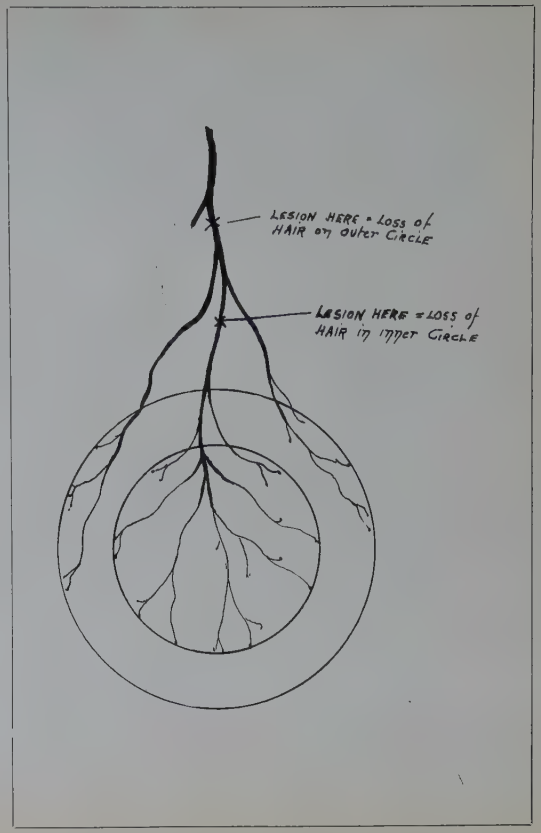


Diagram to Illustrate Nervous Origin of
Alopecia Areata

reaction did not occur when the thigh was rubbed, but by that time the arm reaction had completely disappeared. Thus I succeeded in sensitising my skin to the *P. obconica*. The sensitisation was a general one, although the original inoculation was only made on a very small area.

The second experiment was done on my brother, who also was not previously sensitive to the primula. I wished to try to immunise him by inoculating him several times at intervals of 24 hours on the same principle that antitoxin is now given by repeated small doses so as to avoid anaphylactic symptoms. His left forearm was scraped in the same way as my own, and the crushed leaf of *P. obconica* rubbed in and allowed to dry on. A smaller area was scraped, only $\frac{1}{4}$ inch in diameter. Similar small areas were scraped and rubbed with the primula on 5 successive days at intervals of 24 hours, and twice again at intervals of 48 hours, *i.e.* 7 times in 9 days. The scarified areas were all placed quite close to one another, all within an area of $1\frac{1}{2}$ inch square. None of these areas showed any itching or reaction beyond slight redness round them. Then I waited for 3 weeks, as in my own case, and at the end of that time rubbed the inside of the left forearm with the primula. For 3 days nothing happened, and I was congratulating myself that I had succeeded in producing an immunity, but on the 4th day the skin of the rubbed area became very red and itchy, and a reaction exactly the same as was produced on my own arm appeared and ran an exactly similar course for nearly 4 weeks, with redness, itching, etc. Thus I had produced a sensitisation a second time, but the extraordinary thing about it was the long incubation period of 4 days before the reaction began. In my own case the reaction came on within 12 hours, and evidently the different method used for the inoculations was the cause of the delayed reaction. Six weeks later I again rubbed my brother's arm with the primula, and again he reacted as before, but this time the reaction began to appear in about 12 hours; and a year later, on again testing him, he gave a similar reaction within 12 hours, so that now his skin is in the same condition of sensitisation as my own.

Since doing these experiments on my brother and myself, other 6 individuals (all medical men or students) were inoculated

in the same way as I was myself, but in no case did I succeed in producing any sensitisation. In 3 of these cases the experiment was done twice at intervals. One of these individuals had a distinct family history of asthma and epilepsy, another had suffered some years ago from serum sickness after a second injection of serum given 1 year after the first. In the third, I saw the mother with a typical dermatitis venenata, which was proved to be due to *P. obconica*. In the fourth there was a family history of asthma. In the other 2 there was no history of asthma, urticaria, or eczema to be obtained. In my own case there is a history of asthma on my mother's side, and my mother suffered many years ago from a primula dermatitis. Therefore, out of 8 cases altogether, 2 of whom sensitised, there was a distinct family history of asthma or other sensitisation phenomenon in 6 of them.

Sensitisation once produced seems to last for a very long time, probably for life. It is now over 2 years since I became sensitised, and I still react as before.

My brother also reacted more than a year after he was sensitised. **Hall** mentions a patient, sensitive to *P. obconica*, who avoided contact with the plant for over 20 years, and on touching the plant accidentally at the end of that time suffered again from a dermatitis. Therefore, once an individual's skin becomes sensitive to any substance, it probably remains so for the rest of his life, unless he is artificially desensitised. One attack of dermatitis does not make the individual any less sensitive. On the contrary, he seems to become more so, especially if the attacks follow each other closely.

So far as I can trace, the only other experiments on artificial sensitisation to the primula were done in 1904 by **Nestler** in Germany. He rubbed his own skin with different parts of the plant to see if they irritated. He does not state definitely that he could handle the primula with impunity before he began his experiments, but leads one to infer that he was not affected by it. He rubbed the unbroken skin of the left forearm repeatedly at unstated intervals with the leaves and stalks of the plant and left the juice on for 3 days. He also fixed a part of the plant on to the skin with sticking plaster for some hours at a time, and it was only after 14 days of experimenting thus that he got a marked

reaction to the juice of the plant. In this last application the dermatitis started 40 hours after the plant was applied, and from his description was very similar to that which I produced on my own arm. He also at the same time developed a dermatitis of his fingers because he was still handling the plant as he used to do.

Therefore there can be no doubt that he had sensitised himself, and the interesting point about it is that the sensitisation took place through the unbroken skin. The other interesting fact is that it was only after 14 days of rubbing in the plant at intervals that he became sensitive. That corresponds fairly accurately with the time taken to sensitise animals to a protein, viz. about 10 days.

Nestler also describes several cases of persons who had handled the primula with impunity for years and who suddenly became affected. Among these was a young girl into whose left forearm he rubbed the juice of the primula leaf. As there was no reaction, 6 days later the same area was again rubbed as before, and 10 days after that a severe itchy dermatitis with blistering occurred, and lasted several days. **Nestler** does not give details, but I presume the juice of the leaf was left in contact with the skin and not washed off during that time. Here again it took 16 days from the time of the first rubbing before a reaction began. In yet another case in a man, a dermatitis occurred after the 6th rubbing with the primula leaf at intervals of several days. These 3 sets of experiments of **Nestler**, therefore, have definitely proved that the juice of the primula can penetrate sufficiently through the unbroken skin to cause sensitisation. Also, if the juice of the plant can penetrate in sufficient quantity through the unbroken skin of a sensitised individual to produce a reaction, then there is no reason why it should not penetrate the skin of a normal individual in sufficient quantity to produce sensitisation.

NATURE OF THE POISON PRODUCING THE DERMATITIS

Nestler found that the dermatitis was due to the yellowish-green fluid on the fine hairs of the leaves and stalks. He found that this fluid contained numerous rhomboidal crystals, but did not investigate its chemical composition.

Simpson, in America, extracted the leaves of *P. obconica*, and found that, in addition to protein, they contained an oleo-resinous mixture. The protein part, when isolated and rubbed on a susceptible skin, produced absolutely no reaction. Whereas the oleo-resinous compound, free of protein, gave a very marked reaction on susceptible skin and had no effect on normal skin. **Simpson** also found that the leaves contained 2 active poisons.

1. Needle-shaped crystals which, when powdered and dissolved in water and applied to the susceptible skin, produced a rapid reaction in 30 minutes, increasing in intensity for 8 hours, being still well marked after 36 hours, and then gradually disappearing.

This substance produced no reaction on normal skins. **Simpson** thinks it is a crude glucoside. It did not give the tests for alkaloids, and is probably the crystalline substance seen by **Nestler** in the juice from the hairs on the stems and leaves.

2. The oleo-resinous mixture already referred to, which produced on susceptible skins a reaction which did not commence till after 12 hours, was very intense, spread beyond the area of application, and lasted longer than the reaction produced by the crystalline substance. **Simpson** thinks that the active poison of the oleo-resinous mixture is an acid.

These results agree with what has been found in the various plants of the Rhus family. The most recent authoritative work shows that the active principle of the poison ivy is a substance of a glucosidal nature and not a protein. **Toyama** and others have shown that this substance in the rhus plants is not volatile. Many cases are reported where a dermatitis has occurred without touching the plant, but all the evidence goes to show that these are cases of indirect contact either with objects which had been in contact with the plant or persons who had handled it. **M'Nair** showed that the cases of rhus dermatitis produced by the smoke of burning rhus leaves were due to the solid particles in the smoke, because, if screened through muslin, the smoke had no effect on the skin.

How does the poison get into the skin? The poisonous substance in dermatitis venenata first enters by the hair follicles and glands of the skin. **M'Nair** found in rhus poisoning that microscopically the inflammation was most marked and began

in these areas; but it may, if well rubbed in and left on for some time, penetrate through the horny cells to the deeper layers below. This I confirmed on myself by rubbing the primula juice well into the skin and washing it off with soap and water a few minutes later. That produced a reaction which consisted almost entirely of minute red follicular lesions and not a diffuse erythema such as occurs if the juice has time to penetrate through the whole horny layer.

GROUP REACTIONS

Another point of interest is whether the reactions to plants like the primula are specific. It would seem that they are specific up to a point, but they appear to be of the nature of group reactions. My skin is very sensitive to the *Primula obconica*, but gives a reaction lasting about a week to *P. sinensis*; a lesser but quite distinct reaction to the common wild primrose lasting 2–3 days, and a less reaction still to the coloured hybrid primrose.

I give no reaction to the *P. polyanthus*, *P. auricula*, *P. veris* (cowslip), and *P. malacoides*.

I have also seen an individual whose skin is very sensitive to the jonquil, but who also gives a lesser reaction to the daffodils. There is also the well-known rhus group, all of which are irritating and in certain individuals produce a dermatitis, viz. *Rhus toxicodendron* (poison ivy), *R. diversiloba* (poison oak), and the *R. vernicifera*, which produces the lacquer dermatitis in Japan. The individual reacts most severely to the plant to which he is originally sensitised, and less so to the other plants of the same family. There is evidently some common chemical substance contained in all plants of the same group. This subject will be referred to later in discussing the group reactions which occur in the protein skin tests.

Kanngiesser in 1911 described cases of dermatitis due to *Primula obconica* and also to *P. officinalis* and *P. auricula*. Including 44 cases of his own of dermatitis due to *P. obconica*, he analysed the reports of 191 cases and found that 121 were in females and 70 in males. About one-third of these cases were in gardeners, and of the females nearly all were over 40 years of age. He also noted that fair-haired persons were more often

affected than dark-haired. **Kanngiesser** also reports 2 cases where a bronchial catarrh (asthma ?) was caused by the *P. obconica* being in the room.

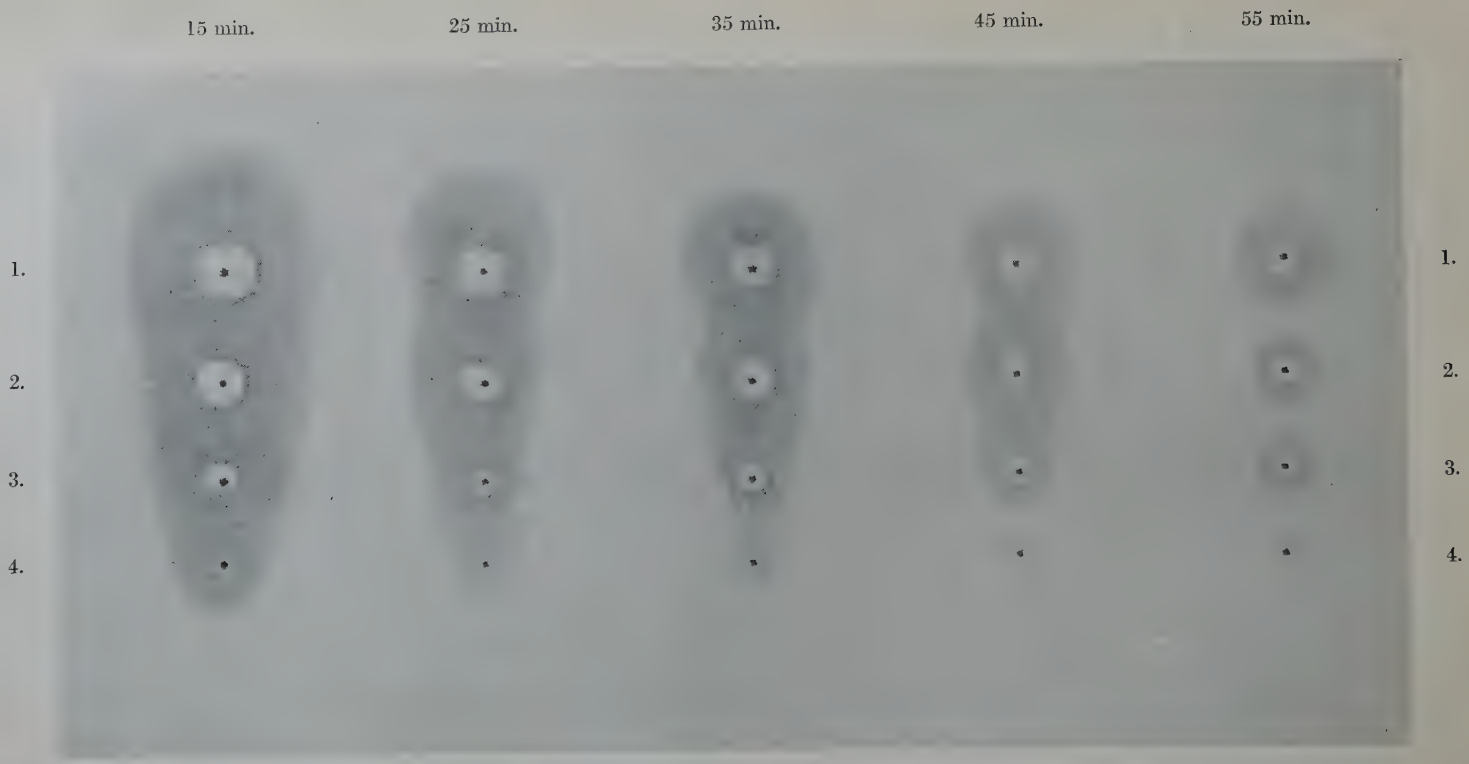
DERMATITIS VENENATA DUE TO CHEMICALS OTHER THAN THOSE CONTAINED IN PLANTS

We have seen that the dermatitis due to plants is not due to proteins, and that, therefore, brings them into line with the dermatitis due to pure chemicals. In all respects these cases of dermatitis are the same as those due to plants; but as the worker in chemicals is always handling the substances and gets them all over his clothing, the eruption is usually much more widely distributed.

In Edinburgh we have an opportunity of seeing a considerable number of these cases, as there are three large firms who manufacture morphine and its compounds, strychnine, and other alkaloids. These firms are constantly having trouble with their workers developing a dermatitis. Some of them develop it within a few weeks of starting work, others have handled the chemicals for 10, 15, and 20 years without developing a dermatitis. In extracting alkaloids such as morphine and strychnine, the crude substances are first put into strong acid, usually sulphuric acid, and this might cause a traumatic dermatitis; but I have satisfied myself by rubbing a case of morphine dermatitis with the crude opium that the skin reacts to that substance. Some years ago **Sir Norman Walker** had a case of dermatitis in an opium worker in his ward. This man had a very extensive dermatitis of head, face, body, and limbs, and it was only after about 8 weeks' hospital treatment that the eruption cleared up. After he was practically well, with the patient's permission, I rubbed the forearm with some crude opium made into a paste with water. This was done at 11 o'clock in the forenoon, and about 6 hours later he developed a very severe dermatitis on the area rubbed, and within 24 hours all the previously inflamed areas of the skin reacted, and he developed an extensive dermatitis very similar to the one which he had on admission, and it took another 3 or 4 weeks before he was able to leave the ward.

In other 2 cases of opium dermatitis I did cutaneous tests

DERMATITIS VENENATA
(STRYCHNIN).



CUTANEOUS REACTIONS TO DRUGS.

1=Codein Phosphate.
2=Heroin Hydrochlor.
3=Morphin Hydrochlor.
4=Control.

with solutions of the alkaloids with which these men worked. Ten per cent. solutions of codein phosphate, heroin hydrochloride, morphine hydrochloride, and morphine alkaloid were used. The one case gave, after 30 minutes, a reaction with wheal formation and erythema round all the areas, but a much more marked wheal round the codein phosphate than round the three others. The other case also gave a very marked reaction to codein phosphate and a slightly less reaction to heroin hydrochloride and morphine hydrochloride (see Plate opposite). These results coincided with what the patients themselves thought, as they both said that codein phosphate irritated their skins more than the other alkaloids and they were always worst after handling it.

Although these are only 2 cases, I think the method is worthy of further use, as it might enable an employer to tell what substances his workers could safely handle.

Plate facing p. 182 shows the hand and forearm of a strychnine worker, but in him the skin test to a solution of strychnine hydrochloride was negative. The cast shows where the test was applied just above the area of dermatitis. Other 2 cases of dermatitis of the hands and arms in strychnine workers were also tested with the skin test, but were both negative. This might be due to the fact that a 1 per cent. solution of strychnine had to be used for the test as stronger solutions cannot be obtained. The positive reactions with morphine were obtained with 10 per cent. solutions, and the reactions to quinine already referred to under drug rashes also only occurred when 10 per cent. solutions were used. Another possibility is that Pirquet's method is not a good one to use. In a case of iodoform dermatitis to be referred to later, the Pirquet test with iodoform was negative, whilst rubbing the skin with iodoform gave a marked reaction. In the next case which I see of strychnine dermatitis I shall rub a larger area of the skin with the strychnine solution or rub it in as an ointment as in Moro's test. Of course, there is always the possibility of the dermatitis being due to irritation from the strong acids used in the preparation of the strychnine, but I think that can be ruled out by the fact that all 3 cases showed a marked œdematous dermatitis of the face as well as of the hands, etc.

I have also tested 3 cases of dermatitis of the face due to

instilling atropin into the eye, and in each case a positive skin test was obtained with a 10 per cent. solution of atropin sulphate.

Therefore I think we are justified in concluding that these cases of dermatitis from chemical substances are sensitisation phenomena of the same nature as the dermatitis due to plants.

Into the same group also fall the large group of dermatitis due to drugs like iodoform, formalin, hair dyes, etc., and in this connection there is the interesting dermatitis which occurred during the war from handling T.N.T. and similar substances in explosive bombs.

Two types of case occurred :—

1. The dermatitis in workers handling trinitrotoluol (T.N.T.).
2. The dermatitis caused by the yellow powder scattered by bursting German bombs.

1. The dermatitis due to T.N.T. was specially reported on by **Cripps, Panton,** and **Ruxton.** The latter found that 32 per cent. of the workers were affected with a dermatitis if no precautions were taken. A few persons were found to be very susceptible to T.N.T., and these were probably cases of true sensitisation to the chemical ; but the majority only suffered from a dermatitis if no care were taken to protect the worker. **Cripps** showed that the dermatitis varied directly with the amount and alkalinity of the sweat. Patients accustomed to take alcohol also suffered more acutely than others. The period between first contact and the onset of symptoms varied greatly. There was found to be no natural immunity to T.N.T. The sweat seemed to make the T.N.T. more irritant either by dissolving it, or the T.N.T. possibly destroyed the fat in the sebaceous secretion and so lessened the protection of the skin. The dermatitis, therefore, in most cases of T.N.T. workers is due to a mechanical irritation which can be eliminated if precautions are taken, so that these cases should be classified as dermatitis traumatica, as they are not true sensitisations. The T.N.T. besides causing dermatitis, by its absorption in some cases, caused abdominal symptoms, irritation of the bronchi, hæmorrhages from mucous surfaces, headache, and giddiness. Cases with purpuric rashes were also recorded, 3 of which ended fatally.

2. Dermatitis from explosive bombs. Cases of this type were recorded by **Ruxton, MacLeod, Sequeira, Cripps, Tyson, Adamson, Thibièrge,** and **Panton.** When the bomb exploded it scattered a fine yellow powder over everything. This stained the skin yellow at the time, and about 9 days later an eruption of closely set vesicles rather like cheiro-pompholyx came out. All the cases reported showed an interval of some days before the rash appeared. These cases seemed to be true sensitisations and the rash appearing after an interval is probably due to the same cause as the rash which occurs in serum sickness. During the 9 days interval the person becomes sensitised, and some of the chemical still circulating by absorption from the skin causes the rash to appear. **Sequeira** states that the substance in the bombs which causes the symptoms is probably hexa-nitro-diphenyl-amine, which is the same substance called " Aurantia " and which **Crocker** described in 1903 as causing a dermatitis in workers who used it to stain cheap leather goods. During the war also many cases of dermatitis occurred from wearing helmets and hats lined with a leather substitute which was stained yellow with aurantia. Such cases were recorded by **Bettmann, Pontopiddan, Schemel, Gans, Baer, Appel,** and **Hellier. Feilchenfeld** also in 1909 described a similar dermatitis produced by wearing gloves dyed with aurantia. In all these cases sweating predisposed to the production of the eruption.

At the dermatological section of the meeting of the British Medical Association at Newcastle in 1921, **Barber** mentioned some experiments which he had done on himself with mustard gas. He rubbed it on his left arm, and it caused a dermatitis. Later, he rubbed it on the right anticubital fossa, and it produced a slough, and a septic lymphangitis ensued. After rubbing the right anticubital fossa, the area on the left arm, where the mustard gas had been previously applied, became red and vesicular. This was evidently a focal reaction in the previous area from absorption of the mustard gas from the left arm.

Innumerable other substances, such as chemicals, dyes, plants, etc., have been reported as causing a dermatitis in certain individuals. Space will not permit me to give a full list of all the possibilities, but probably any substance may lead to a dermatitis under certain circumstances. I shall briefly refer to some of the

commoner ones and record some cases due to substances not previously known to cause dermatitis.

Amongst plants the Primulæ, and especially the *Primula obconica*, are probably the commonest in this country. Other plants which commonly cause trouble are the Virginia creeper (*Ampelopsis Hoggii*), common ivy, *Humea elegans*, daffodils, hyacinths, and other bulbs. The following have also been recorded within recent years :—

Eucalyptus plant and oil (**Galewsky**).
Quercus Robur (oak) (**Spillmann**).
Geranium (**Anderson**).
Cotton-seed (**Nixon**).
Chrysanthemum (**Waugh**).
Satinwood (**Bidie, Cash, Jones, Siegheim, Wechselmann**).
Lycopersicum exulentum (tomato) (**Lain, Washburn**).
Anthemis Cotula (Mayweed) (**Sequeira**).
Lillies (**Walsh**).
Bitter orange (**Murray**).
Arundo Donax (reed) (**Timpano**).

In America the rhus plants are the commonest irritants and belong to the same family as the *Rhus vernicifera* which causes the lacquer dermatitis of Japan. This lacquer is used for varnishing boxes, walking-sticks, etc. Ragweed (**Sutton, J. C. Walker**), cactus (**Sutton**), Timothy grass pollen, flax-seed, and many others have been reported in America as causing dermatitis.

Pardo-Castello also collected more than 40 species of plants, chiefly of the genera Anacardiacea, Legumenosæ, Euphorbiaceæ, and Urticaceæ, which cause different degrees of dermatitis in the Tropics.

From time to time what might almost be called epidemics of dermatitis occur due to chemical irritants in clothing, etc. Of these the commonest are the following :—

Hair Dyes.—The commonest hair dye to cause dermatitis is paraphenylene-diamine. It is sold under the name of "Inecto Hair Dye." I have seen several cases due to it, and **Barker, Bunch, Burke, Brocq, Cathelineau, Harrington** and **Gold, Mackay, Mewborn, Shalek, Tirsot,** and **Wood** have reported cases. This hair dye was sold widely in America some years ago as "Mrs Potter's Walnut Juice Hair Stain." In most cases the dermatitis

only occurs after several applications, but occasionally it irritates on the first application. The " Inecto " dermatitis is evidently a true sensitisation of the skin. In some cases, by absorption, general symptoms of poisoning have been produced.

Dyed Fur Dermatitis.—Within recent months very numerous cases of dermatitis on face, neck, and wrists have occurred in Edinburgh and elsewhere due to an artificial beaver fur (dyed coney) worn on the collars and wrists of ladies' coats. **Semon, Roxburgh,** and **Castle** have recorded cases. In a report which I received on this kind of fur from the manufacturers, they stated that the dye used was quite harmless as it only consisted of paraphenylene-diamin ! It is a question whether these cases are true sensitisations as they occur very readily if the fur becomes wet either by rain or by perspiration from the neck or wrists. Some seem to be true sensitisations, but many seem to be the same type of dermatitis as occurs in T.N.T. workers.

Match-Box Dermatitis.—This form of dermatitis was first described by **Rasch** in 1918. It occurs chiefly in men and usually begins on the front of the upper part of the left thigh owing to carrying a match-box in the trouser pocket. It may also occur on the right thigh if the box is carried on that side. It may spread on to groins, genitals, and even the lower abdomen, and by handling the boxes the hands may be affected, and the face through the hands. The lesions are those of an erythematous and œdematous dermatitis.

Christiansen also described cases in Sweden ; **Frei, Strandberg,** and **Stranz** in Germany ; and **White** and **Fox** in America. So far as I can ascertain no cases have been recorded in this country. This condition did not occur till 1918, when the match-box manufacturers in Sweden and Denmark added phosphorus sesquisulphide (P_4S_3) to the amorphous phosphorus usually used on the striking surfaces of match boxes. It was added during the war as a substitute for some of the ordinary phosphorus, and seems to cause the dermatitis by the heat of the body vaporising the sesquisulphide either pure or in some other form. The reaction is a quantitative one rather than a qualitative one. **Frei** did a great many experiments by scraping the substance off the side of the match boxes and testing his own skin and that of persons who had had the dermatitis and also those not

previously affected. If this substance was applied for 24 hours to the skin of anyone who had previously had the dermatitis, it produced redness and irritation with swelling of the skin. In 140 healthy persons or persons suffering from other diseases, in only 2 did he get an irritation of similar extent to that of the previously affected cases. In the great majority of cases there was no irritation or only a slight redness after 24 hours' application. But in a good many cases, if the substance were continuously applied for several days, an irritation was produced. **Frei** found on experimenting on himself that areas which were previously inflamed were more easily irritated on a subsequent application. Therefore this form of dermatitis does not seem to be due to a true sensitisation of the skin. Most individuals seem to get a reaction if the substance is applied for a sufficiently long time or rubbed sufficiently well in. It therefore should be classed as a dermatitis traumatica. A previously inflamed area reacts more readily to subsequent application, so that there is a local increased sensitiveness such as occurs in all forms of dermatitis traumatica.

Insecticide Powders.—**Reeb, Fujitani, M'Donnell, M'Cord, Kilker,** and **Minster** report cases of dermatitis due to powdered pyrethrum used as an insecticide. The latter observers report it in the workers making the powder, many of whom suffered from a mild dermatitis, especially in summer when they perspired freely, but some of the cases were apparently real sensitisations.

Tar Dermatitis.—Apart from the chronic dermatitis caused by tar, dermatologists frequently find that tar irritates certain skins. In 1921 I saw a case where sensitiveness to tar developed during treatment. He was treated for psoriasis in April 1920 with crude coal tar on the body and pix carbonis in acetone on the scalp. The tar caused no irritation. In February 1921 he was seen again with an acute dermatitis on the scalp, face, and arms where he had again applied the tar as the psoriasis had recurred. He was tested by painting a small area of one arm with crude tar, and reacted violently with a marked dermatitis which lasted several days. During the first course of treatment this man had evidently become sensitised to the tar and reacted some months later when it was reapplied.

Other chemical substances reported as causing dermatitis are—

Rubber adhesive plaster containing agathis damara (**Kuack**).
Procain used by dentists (**Lane**).
Oil of citronella used as preventative of mosquito bites (**Lane**).
Anilin dyes in workers and from clothes dyed with these (**Landowzy** and **Bronardell, Blaschko, Balzer, Wilson, Sachs, White**).
Scharlach R. (**Lombardo**).
Formalin (**Galewsky**).
Phenyl-hydrazin (**Hall**).
Hairy caterpillars of the moth, *Euproctis Edwardii* (**Cleland**).
Copra (**M'Leod**).
Printer's ink (**M'Connell**).
Dinitro-benzol (**Bernstein**).
Hemamethylamine (**Shepard** and **Krall**).

Various other forms of dermatitis, many of them of the nature of folliculites, are recorded in metal workers using irritating oils (**M'Lachlan**) and in linen spinners (**Leloir**), but these do not appear to be sensitisation phenomena.

Adamson and **Cooke** also report cases of dermatitis in the napkin area of infants and in children with enuresis due to ammoniacal urine. **Cooke** isolated a gram-positive bacillus which caused fermentation of urea with the production of ammonia. The dermatitis seems in these cases to be due simply to the irritation of the ammonia.

In my own practice within recent years I have seen cases of dermatitis due to the primula, daffodils, Inecto hair dye, dye used by wool-workers, dyes in furs, morphia, tar, iodoform, lysol, formalin, kresol, atropin, *Humea elegans*, enamel used to glaze porcelain, and guinea-pig's hair. To the above list I should like to add 3 cases of dermatitis due to substances which have not hitherto been reported as causing irritation.

1. Last autumn I saw a medical man with a very marked dermatitis venenata of hands and face. He was on holiday at the time in the Highlands. I told him to test himself by rubbing the arm with the different plants with which he had been in contact. He found that he gave a very violent reaction to bell heather, but not to the ordinary heather.

2. Another case was a farmer who developed a severe dermatitis after handling sheaves of oats. He gave no reaction on rubbing oatmeal into the skin. Later he had another attack after handling sheaves of barley, but he gave no reaction when tested with barley. So I told him to look out for weeds in the sheaves and he found that milfoil (*Achillea millefolium*) was present and it, when rubbed on the skin, gave a very marked reaction.

3. The third case was in a working housekeeper who had had a dermatitis of hands and face every year for 15 years beginning in October and lasting till about February. She was completely free all the rest of the year. I asked her to keep a look-out next year when the dermatitis began, and she found that it was due to plucking grouse. As soon as she stopped touching the grouse feathers the dermatitis rapidly disappeared. This patient also showed a group reaction as her skin reacted slightly to the feathers of other game birds such as partridges and pheasants, but not of the common fowl.

GENERAL AND LOCAL SENSITISATION

In these various forms of dermatitis venenata already referred to, it has been seen that the phenomenon is a general one affecting the whole skin surface. This, however, does not apply to the mucous membranes. I can rub the primula leaf on the mucous membrane of the mouth and nose without producing any reaction. **Jadassohn** also found, in iodoform dermatitis cases, that iodoform had no effect when applied to mucous surfaces. I saw a case in the gynæcological wards some months ago, where, after an operation on the uterus, the vagina was packed with iodoform gauze. This patient next day showed a very marked dermatitis of vulva, groins, and lower abdomen, and on testing her later on the skin of the arm she reacted markedly to iodoform. Yet the mucous membrane of the vagina showed no change, although the iodoform had been in contact with it for over 24 hours. Therefore the absence of reaction on the mucous surface was not due to the moisture of the surface keeping the chemical from getting into proper contact, as might be the case if it were only applied for a short time.

Also many persons with poison ivy dermatitis have chewed

the leaves and swallowed the juice without suffering any inconvenience.

Bloch repeated **Jadassohn's** experiments on a patient sensitive to iodoform. He found that subcutaneous injection of iodoform oil (avoiding the skin), internal administration of iodoform, or application to mucous surfaces for 24 hours had no effect, but as soon as a trace was applied to the skin a dermatitis resulted. Therefore he concludes that the cases are not a true general anaphylaxis, not a humoral condition, but a cellular hypersensitiveness. To confirm this he transplanted a piece of skin from this iodoform dermatitis case and also a piece from his own skin on to another person with a healing burn. When both pieces had "taken," he dusted the area with iodoform and obtained a very marked reaction only on the piece of skin from the patient who was sensitive to iodoform. The rest of the skin, including the piece of **Bloch's** own skin, showed no reaction. **Bloch** and **Massini** also did similar experiments with extract of ringworm fungus (p. 136). **Bloch,** who was himself sensitised to an extract of the ringworm fungus (trichophytin) and whose skin gave a positive trichophytin reaction, transplanted on to a patient with chronic leg ulcer a piece of his own skin and a piece from a normal individual not sensitive to ringworm. After the 2 pieces had taken, he did cutaneous tests with trichophytin on this man —on the normal skin, on the piece transplanted from **Bloch's** own arm, and on the piece transplanted from the normal man's arm—and obtained a positive reaction only on the piece of skin transplanted from his own arm.

These experiments prove conclusively that in sensitisation of the skin the condition is a cellular one of the cutaneous epithelium and does not depend on the blood or other organ.

IS DERMATITIS VENENATA A TRUE ANAPHYLAXIS?

Most workers on anaphylaxis hold the view originally stated by **Richet** that true anaphylaxis can only be produced by a protein. **Ford** claims to have produced it by a glucoside, but doubt is thrown on the purity of his antigen by **Stevens, M'Nair,** and **Warren. Zinnser** states that in true anaphylaxis not only

are specific antibodies present in the blood, but the production of passive anaphylaxis in animals shows that the antibody originating and residing in the fixed tissue cells must necessarily circulate in the blood stream. **Simpson** holds that although in primula dermatitis we are dealing with an example of hypersensitiveness to a chemical, the requisites of anaphylaxis are not fulfilled, and has shown that it is not possible to sensitise an animal actively to the poison of the plant or passively with the serum of a susceptible individual. He also found that no specific amboceptors are present in the blood of susceptible persons, and that the protein of the plant has nothing to do with the reaction. That being so, it is as impossible to produce an antitoxin to the poison of the plant as it is to produce a condition of specific sensitisation not dependent on circulating toxins. Antibodies, if concerned in the reaction, are present only in the sensitive cells. These antibodies, however, must be carried by the blood stream in order to sensitise the cells. This was proved by the fact that by rubbing a small area of my skin with the *Primula obconica* I sensitised my whole skin.

Bruck did a number of experiments with iodoform to try to show that iodoform dermatitis was a true anaphylaxis. He injected 3 guinea-pigs with 5 cc. serum from a patient who showed a dermatitis when iodoform was applied to his skin. Twenty-four hours later 0·3 grm. of iodoform was injected into each guinea-pig, and within 5 minutes 2 of them showed typical anaphylactic symptoms and the other showed some dyspnœa only. Control animals injected first with normal human serum and horse serum, and then with iodoform, were all negative. Therefore he concluded that passive anaphylaxis could be produced. But by using the serum of another case of iodoform dermatitis **Bruck** did not succeed in causing anaphylaxis in guinea-pigs. **Bloch** and others have questioned the validity of **Bruck's** results, as the symptoms in the guinea-pigs might not be due to true anaphylaxis but to iodoform poisoning, which causes symptoms of an anaphylactoid nature. **Bloch** repeated **Bruck's** experiments, but failed to produce passive anaphylaxis in guinea-pigs with the serum of cases of iodoform dermatitis, so that there is no definite evidence yet that in dermatitis, such as that produced by iodoform, there is a real general anaphylaxis.

The only reference (apart from *Rhus toxicodendron* cases) which I can find to any fatal result in dermatitis venenata is a report by **Brown**. In his case the patient accidentally scratched her nose whilst smelling a plant of *Primula obconica*. The nose rapidly swelled and a carbunclelike lesion appeared with œdema of the face and head. Death followed in a few days from pneumonia. This fatal result cannot, however, be attributed to the dermatitis. The nose lesion was scraped under an anæsthetic, and it is quite probable that the death was due to septicæmia. **Brown** also mentions 2 other similar cases of infection from *P. obconica*, one of whom also died and the other recovered after a prolonged illness. It is the usual clinical experience of dermatologists that œdematous dermatitis of the face from the primula looks somewhat like erysipelas, and to an inexperienced observer cases of erysipelas might be mistaken for a dermatitis venenata.

Rhus toxicodendron, however, is well known to cause serious poisoning. **White** reported a case of a boy aged 6 years who was twice poisoned one summer with *R. toxicodendron*. Next year a boy known to be insusceptible to rhus was employed to tear up some rhus plants. The boy subsequently washed his hands in hot water and soap, and later with vinegar. He was watched to see that the washing was thorough. In the afternoon the boy took the susceptible child to a pond to bathe. Having stripped him he took him into the water, holding him by the arm-pits, and afterwards massaging his back with his open palms. Two or three days later the child was taken ill and grew rapidly worse. Deep ulcers appeared under the arm-pits, and the skin of the back showed in an aggravated form the usual appearances of poisoning with ivy. The child died at the end of 3 weeks. Such cases of extreme sensitiveness, however, are rare, considering the number of cases of rhus poisoning which occur.

LOCAL SENSITIVENESS OF THE SKIN

In addition to the general epithelial sensitisation there are undoubtedly cases where you get a local sensitiveness of the skin. At Newcastle last year **Barber** mentioned such a case in a baker, whose hands and forearms, but not the rest of his skin, reacted on application of flour.

De Jong, in 1923, drew attention to the fact that dermatitis in bakers is often due to the strong salt solution which is added to the flour before baking. The heat in the bakehouse causes the salt to crystallise on the arms, and in kneading the bread the crystals are rubbed into the skin and so produce a dermatitis. These cases are not, therefore, cases of true flour dermatitis and should be separated from them. **Markley** also reports a dermatitis of face, neck, chest, arms, and hands from handling a guinea-pig. The patient's skin reacted only when guinea-pig's hair was rubbed on these areas and nowhere else.

Recently I saw a lady with a similar dermatitis on the neck where a pet guinea-pig was in the habit of lying, but I had no opportunity of testing this patient to see whether the skin was sensitive all over or only on the neck.

There is also the well-known experiment with tuberculin by **Pirquet** on his own arm. He found that the skin of the left arm, which he habitually used for experiments, was sensitive to a tuberculin of a dilution of 1 in 1000, whilst the skin of the right arm was negative to tuberculin 10 times as concentrated. It may be that in these cases the skin is sensitive all over, but the degree of sensitiveness may vary in different places. On the other hand, it may not be a sensitisation phenomenon at all, but merely a mechanical irritability of certain areas of the skin to a repeated or prolonged application of some chemical substance. They are similar to the washerwoman's dermatitis of hands and forearms. In such cases one does not get lesions on the face, even although the skin there is frequently touched by the hands. I think a distinction should be made between this group of cases and the true dermatitis venenata. **Whitfield's** term of dermatitis traumatica seems to be the most appropriate one.

A good deal of experimental work has been done with regard to the tolerance of the skin to local irritation. In 1892 **Samuel** found that repeated application of croton oil to a rabbit's ear produced a relative immunity, so that the skin after recovering from the first application did not react so violently to a second application of the croton oil. Also, such an area of skin after recovering from a croton dermatitis reacted less markedly than normal skin to other irritants, such as the application of hot water, etc. **Fürst** likewise, in 1898, by repeated freezings and

scaldings of the skin at intervals, so changed the skin that the same irritants produced after a time practically no inflammation.

Schaer, in 1907, repeated **Samuel's** experiments on rabbits' ears with silver nitrate, cantharides, turpentine, etc., and obtained the same results, *i.e.* a relative immunity, not only to the substance which produced the original dermatitis, but also to other irritants.

So also **Stein,** in 1909, succeeded in producing a skin tolerance to irritants applied in gradually increasing concentrations, and also found that the tolerance was not specific for each irritant. **Stein** thinks it is due to some alteration in the epithelial cell, whereas **Samuel** put the change down to an alteration in the blood-vessels of the skin.

Schultz, in 1912, tested the effect of different strengths of carbolic acid on the skin in different diseases, and found that in eczema the whole skin showed an increased sensitiveness to the carbolic.

In 1920 **Auer** found that if a rabbit was sensitised to horse serum, the skin of its ear reacted much more violently to the application of a substance like xylol than did normal control animals. He explains this as due to the local irritation of the xylol causing inflammation and an exudation into the part. In a recently reinjected animal the antigen is still circulating in the serum, and when the serum passes out into the skin, from the irritation of the xylol, a local hypersensitive reaction is produced.

Ferguson Smith repeated **Auer's** experiments on sensitised rabbits, using cantharides and croton oil instead of xylol as the irritant. He found that " no dilution, which fails to provoke a visible reaction in a normal rabbit, will provoke one in an anaphylactic animal." This observation tends to throw doubt on **Auer's** results, but if **Auer's** work is to be taken as valid, then his experiments together with **Schultz** would seem to indicate that in a condition like washerwoman's dermatitis the patient works for years with soap and soda with no ill effect—in fact, acquires often a considerable degree of tolerance to these substances. The same patient, if she becomes sensitised to some antigen, say, from internal absorption or elsewhere, possibly not sufficiently so to produce any symptoms, may get a local reaction in the skin of the hands from the soap and soda causing

an exudation, and thus bringing sufficient circulating antigen, through the serous exudate into the skin of these parts, to produce a reaction.

Burns of the skin may be included under the heading of dermatitis traumatica, but a number of experiments performed in 1912 by **Alhaique** are suggestive that in severe burns a process of sensitisation may occur. He burned rabbits by applying hot water at a temperature of 80°–100° C. for 3–5 seconds, and found that animals which had recovered from a previous burn became more susceptible to the action of a second burn. They often died with symptoms like anaphylaxis from the effects of a second burn which was not of an intensity or extent to cause death usually. Animals sensitised with serum from a previously burned animal showed on reinjection with the same serum phenomena which **Alhaique** attributed to a state of anaphylaxis. He thinks that a burn causes the absorption into the circulation of toxic substances which sensitise the individual, and that many of the late deaths from burns can be explained on this theory.

IMMUNITY AND DESENSITISATION TO DERMATITIS VENENATA

Ford, in 1907, experimented with the rhus poison and found that he could produce a real antitoxic immunity to it by repeated intravenous injection. He thinks that there is a reasonable possibility that the use of an antitoxic serum may acquire a definite place as a practical therapeutic measure in the treatment of severe cases of rhus dermatitis. **M'Nair** says that natural immunity to the rhus plant is seldom absolute. If sufficiently vigorously applied he always produced a reaction. In my experiments with the primula in those who did not sensitise, possibly I did not rub the antigen in sufficiently vigorously or over a sufficiently wide area.

In the experiment on my brother by repeated daily inoculation the result was sensitisation, with a delayed incubation in the first instance, and not an immunity as I had expected. I did not pursue this line of investigation further, because, even although I had immunised someone, it would have been impossible to say whether that individual had been made immune or whether he

was naturally so. But if I were repeating the experiment I should inoculate the skin at very short intervals, say, every half hour, for several times in the same way as serum injections are given by splitting the dose and giving at short intervals so as to cause desensitisation.

One attack of dermatitis venenata does not produce an immunity or desensitisation to further attacks. There are numerous cases in the literature of poison ivy dermatitis cases, who, as soon as they were cured of one attack, immediately got another on touching the plant. Therefore, any attempt to desensitise patients by repeated applications of the irritant are not likely to be successful. On the other hand, either ingestion by the mouth or desensitisation by injections are more likely to prove efficacious.

Strickler, Duncan, Dakins, and others quote numerous cases where chewing the leaves of the poison ivy and swallowing the juice each spring rendered the individuals immune at least for that season. **Schamberg** also confirmed this, and found that the administration of a fluid extract of the plant by the mouth was quite successful, if the extract was taken in gradually increasing doses for about a month.

Much experimental work has also been done by **Strickler, Petch,** and **Alderson** by injections of extracts of the poison ivy and oak. **Strickler** claims that intramuscular injection of the toxin of *Rhus toxicodendron* can cure the dermatitis of poison ivy, the inflammation and itching being greatly modified within 24 hours after the first injection. A second injection 24 hours later as a rule was sufficient to cure a case. This result is a desensitisation and not a true immunity as it is only temporary. **Strickler** recommends intramuscular injections during the attack and subsequent administration of the extract by the mouth later on to keep up the desensitisation.

Diffenbach reports the production of immunity to the poison ivy by drinking milk of cows fed on grass and poison ivy.

A man suffering from a dermatitis due to ragweed pollen was given by **Sutton** 12 injections of an extract of the pollen in gradually increasing doses. This removed his susceptibility so that he could handle ragweed with safety. **Hannah** also reports a successful result by the same extract in a similar case.

Therefore desensitisation to plant dermatitis can be successfully accomplished by oral administration or injection of the plant or extracts from it. This desensitisation is not, however, permanent, as the workers with *Rhus toxicodendron* showed that the desensitisation only lasts for about 2 years.

Conclusions

1. It is possible by rubbing the juice of a plant such as the *Primula obconica* into the broken or unbroken skin to sensitise the skin to that plant.
2. The sensitisation in such cases is general over the whole skin.
3. Such sensitisation is not due to the protein of the plant but to a substance of a glucosidal nature.
4. The reactions to plants are relatively specific and are of the nature of group reactions.
5. Sensitisation of the skin may occur to pure chemicals such as morphine, etc.
6. Dermatitis due to bell heather, *Achillea millifolium*, and grouse feather are described for the first time.
7. Dermatitis may be a true sensitisation, *i.e.* dermatitis venenata, or simply due to irritation, *i.e.* dermatitis traumatica.
8. The sensitisation is a sensitisation of the skin cell only, and is not a true general anaphylaxis.
9. A true local sensitisation of the skin may occur.
10. Desensitisation has been successfully accomplished to plant dermatitis by oral administration of the plant or injection of extracts from it.

CHAPTER XI

DERMATITIS OTHER THAN D. VENENATA AND D. TRAUMATICA

This large group may be divided into the so-called " Eczema " and Seborrhœic Dermatitis.

DERMATITIS—ECZEMA

This group includes all forms of dermatitis where no definite external cause can be demonstrated. The term " eczema " will be used frequently so as to avoid confusion. Although I do not like the name, and prefer the term " dermatitis," for the sake of convenience I shall use it because the word dermatitis to some minds includes dermatitis venenata and dermatitis traumatica, which are excluded from the eczemas. We are not concerned here with the clinical varieties, such as erythematous, papular, vesicular, weeping, crusted, squamous, etc., but with the evidence for or against sensitisation being responsible for them. The older theories may be roughly divided into :

1. *Toxic Theory.*—This was strongly advocated by the French school of dermatologists, the gouty, arthritic, and other forms of diathesis being held responsible for the condition. There is, however, no direct evidence of toxins causing the condition, although they may indirectly predispose to it.

2. *Neurotic Theory.*—The fact that attacks of dermatitis may result from or be aggravated by anxiety, shock, worry, etc., has been held to support its nervous origin, but, as in the previous theory, while it may predispose to attacks there is no direct evidence to support this theory. The frequency of dermatitis in infants, where the influence of the nervous system may

presumably be to a large extent excluded, is also very much against its acceptance.

3. *Bacterial Infection Theory.*—This theory, especially urged by **Unna,** is now generally considered as being untenable. All the evidence goes to show that the condition is not contagious, and that any organisms present in the lesions are secondary infections.

None of the above theories explain the phenomena satisfactorily. The fact that dermatitis venenata, which shows a practically identical clinical lesion and is a sensitisation phenomenon, at once suggests that all forms of eczema are sensitisations. **Fordyce** was the first to suggest that eczema is anaphylactic. Its association with asthma, which may be taken as definitely proved to be a sensitisation phenomena, and the work done on asthma point to a similar origin for the two conditions. Although not an inherited disease, **Van der Veer** and others have pointed out that in certain families asthma, urticaria, and eczema are much more frequent than in others. As I showed under dermatitis venenata, only certain individuals have skins which are readily sensitised, and, therefore, the hereditary factor is important.

The actual proof that eczema is a sensitisation phenomenon will necessarily be a difficult one, but the more one thinks over the subject the more one is driven to the conclusion that it must be so. The changes in the skin in eczema are identical with those of dermatitis venenata. The eruption flares up and dies down again in the same way as it does in dermatitis venenata after each application of the irritant. All the conditions which have been shown to be present in the skin cell in dermatitis venenata may be assumed to be present in eczema.

Weidenfeld made an extensive study of the reaction of the skin of eczema patients to irritants, using dilutions of croton oil. He found that the skin of eczema patients shows a greater reaction than normal skin, and the more acute the disease the greater the reaction. The strength of the reaction was found to decrease as the disease disappears. The increased sensitiveness lasts for some time after recovery, but is always transitory. The normal skin near the eczematous patch showed a greater reaction than that at a distance. The skin of a healed patch was more sensi-

tive than the skin which had never been affected. **Weidenfeld** thought that the increased irritability of the skin is due to toxic substances passing from the primary eczema patches into the blood and causing changes in the skin which predispose to eczema. This irritability of the skin in eczema, however, can be explained on the sensitisation theory. The croton oil by irritating the skin and producing a hyperæmia brings a larger quantity of circulating antigen to the part, and a reaction takes place between the antigen and the sensitised skin cells. It is the same phenomenon as has already been referred to under dermatitis venenata in the experiments which **Auer** made with xylol (p. 195).

Schultz, in 1913, confirmed **Weidenfeld's** results, using phenol as an irritant.

Jaeger, in 1923, also came to the same conclusion, using formalin, oil of turpentine, and tinct. arnicæ as irritants. He found that in over 50 per cent. of the cases of eczema the skin responds to the external application of these irritants with a more intense reaction than is seen in normal skins. This reaction was found in infantile, professional, seborrhœic, and so-called constitutional eczemas.

Ferguson Smith, however, in 1923, could not confirm the results obtained by **Weidenfeld, Schultz,** and **Jaeger.** He tested the skin of 50 eczema patients, using dilutions of cantharides and croton oil as irritants. He "failed to discover any notable and constant increase of sensitiveness."

Further experiments are, therefore, necessary to clear up this matter.

Harris, discussing the work of **Weidenfeld** and **Schultz,** did not agree that the irritability of the skin in eczema to irritants resided in the epithelial cells as it varies so much. He thought it more probable that the nervous system is responsible. The irritability of the skin can be diminished experimentally by adrenalin applied either externally or subcutaneously. Assuming that eczema was a protein sensitisation, and possibly similar to sensitisation which can be produced with histamin (p. 13), **Harris** made experiments to find out the frequency with which histamin is found in the stools in cases of eczema. Histamin is a product of pancreatic digestion. Unfortunately **Harris's** death occurred before these experiments were completed.

THE INFLUENCE OF THE NERVOUS SYSTEM ON ECZEMA

That the nervous system plays an important part in eczema is undoubted. **Morris** and others have reported cases where anxiety, worry, etc., have precipitated attacks or aggravated existing eczemas. The itching, which is so constant a feature of the disease, also points in the same direction. **Samuel,** in his experiments, showed that when the sensory nerves supplying the ears of rabbits were cut, scalding did not cause inflammation. **Bruce** showed that cutting the nerves to the conjunctiva prevented inflammation when mustard oil was put in the eye. **Spiess** noticed that, after tonsillectomy, if the denuded area were anæsthetised, the inflammatory reaction and swelling were distinctly less or absent, and the wound healed more quickly than it did if not anæsthetised.

All these facts go to show that nervous reflexes are necessary for the production of inflammatory reactions, and that the nervous system is necessary before an inflammation like eczema can occur. It has already been shown that the nervous system plays a part in carrying out the various phenomena of a true anaphylaxis, and similarly it does so in all sensitisation phenomena.

Similarly, the endocrine glands are intimately bound up with the sympathetic nervous system. **Edelman** reports a case of eczema in a child of $3\frac{1}{2}$ years of age. The disease had been present since the age of 4 months. The child showed signs of thyroid deficiency, and the eczema rapidly disappeared on the administration of thyroid extract. **Harris** suggested that in eczema some toxic substance in the blood neutralised the suprarenal secretion and so affected the nervous reflexes of the skin. In support of this, he quotes the frequent association in eczema of low blood-pressure and asthma, both of which conditions are counteracted by adrenalin.

Moro, in 1920, published an article on the hyperexcitability of the vegetative nervous system and changes in the endocrine glands at certain seasons of the year. In 237 cases of infantile eczema the incidence of the first eruption was highest in January, February, and March. From April it gradually decreased till August, when it gradually rose again till December. Of these

237 cases 4 died, 3 in March and 1 in April. **Feer** also reports 11 deaths from eczema, 9 of which occurred in February, March, and April. The cases which were examined post-mortem showed no pneumonia, so that the deaths were not due to chills.

Moro also quotes **Hamburger,** who found that tuberculin hypersensitiveness was higher in spring than in autumn. He also states that cases of tetany occur most frequently in the spring. He concludes that in spring there is a change in the endocrine glands and vegetative nervous system which makes infants more susceptible to attacks of tetany and eczema.

The sympathetic nervous system and the endocrine glands, therefore, would seem to play a part in eczema as they do in true anaphylaxis.

PASSIVE ANAPHYLAXIS IN ECZEMA

Blackfan attempted to produce passive anaphylaxis in guinea-pigs by injecting them with the blood serum of patients with eczema due to egg white and cow's milk, but failed to obtain any result. **Schloss**, however, claims to have done it successfully with the blood serum of sensitive patients.

FOODS IN ECZEMA

It has been known for a long time that in some cases of dermatitis alteration of the diet has resulted in a cure of the condition. The connection between the diet and the eruption of dermatitis is not so evident as it is in some cases of urticaria. Most of the work done in this connection has been done in infantile eczema where the diet is less complicated and more easily controlled than in adults. Some hold that excess of certain food constituents in the diet will cause eczema, others support the sensitisation theory, basing their evidence chiefly on the sensitiveness of the skin to certain foods, as demonstrated by the food skin tests. These reactions will be fully discussed later under cutaneous reactions.

Fischer thinks that there is an association between gastric and gastro-intestinal derangements and eczema in infants, as acute eczema may follow overfeeding with fats and carbohydrates.

He states that eczema is more frequent in bottle than breast-fed infants. Undigested particles of food give rise to fatty acids, and these, when absorbed, cause a toxæmia which results in skin irritation and dermatitis. Feeding with large quantities of cream gives rise to fat indigestion. Similarly, excess of sugar and carbohydrates may be factors in the etiology of eczema. He quotes cases of eczema infants who were given all kinds of food which they could not digest. They all recovered as soon as they were put on a diet of buttermilk, vegetables, and fruit juices.

Talbot and **Towle** also demonstrated in infantile eczema that there is an incomplete digestion of fats and carbohydrates. **Morse** reports a case of infantile eczema associated with constipation and an excess of fat in the diet.

Johnston found that in about 40 per cent. of cases of eczema in adults hyperacidity was the most common digestive disorder. Indicanuria, which indicates intestinal fermentation, is also frequent, and constipation is often present. He found that in eczema there is no constant failure in the synthesis of urea, and showed that there is no proof that there is any constant error of metabolism.

White examined the stools in 46 cases of eczema, and found that 28 per cent. had normal fæces, 63 per cent. had excess of fat, and 8 per cent. excess of starch. When both skin tests and fæcal examinations were made in the same individual the 2 methods did not always reveal similar results. In the patients with normal stools one showed a positive skin test to all types of food, and another to fat. In those with fat in the stools 10 showed negative skin tests to all foods and 2 were positive to starch. In the starch-stool group 1 gave wholly negative skin tests. Therefore mere inability to digest and assimilate certain types of food does not necessarily mean that the individual has become sensitised to these foods. On the other hand, sensitisation to a food or foods as shown by skin tests may occur where the digestion is apparently normal.

These observations naturally lead on to the further question as to whether altered digestion does not lead to absorption of undigested proteins into the circulation so as to cause sensitisation. A great deal of work has been done in this connection. **Van Alstyne** showed that in dogs, egg albumin introduced into

the stomach or any part of the small intestine, except the duodenum, passed unchanged into the blood stream. The same results were also obtained with ox and beef serum. It is now possible by the precipitin and anaphylactic reactions to distinguish proteins in very small quantities in the circulation. At first it was thought that in digestion the proteins were split into proteoses and peptones and in that form entered the circulation. These substances are soluble and can permeate parchment membranes. Further experiments by **Underhill** showed that peptone and proteoses, if introduced direct into the blood, were highly toxic, and **Howell** demonstrated that after a heavy protein meal the blood serum shows no excess of proteoses, and that the blood of the portal vein during the period of maximum absorption after a meal shows no proteoses or peptones. Recent investigations show that the splitting of proteins before absorption proceeds much further than was supposed. They are split into amino-acids, in which form they are found circulating in the blood.

Falls quotes **Abderhalden** as stating that the liver is the buffer between the intestine and the general circulation, and protects the latter from the entrance of foreign proteins in an undigested state. The liver is probably rich in ferments (as shown by post-mortem autolysis), and these ferments probably change the absorbed proteins into substances which can with safety be thrown into the general circulation.

Van Alstyne used the anaphylactic shock test to demonstrate the presence of unchanged proteins in the circulation. The protein was introduced into an isolated loop of intestine, and after an interval blood was withdrawn and introduced into a guinea-pig previously sensitised to that protein. If the animal developed anaphylactic shock, it was taken as proof of the presence of unaltered protein in the blood. **Van Alstyne** showed that conditions which interfere with normal digestion, such as ligaturing a portion of the intestine, increase the amount of protein absorbed.

Nathan quotes **Lesné's** work, in which the latter showed that egg albumin injected into a sensitised animal induces anaphylaxis even after it had been digested with pepsin. But when the egg albumin had been subjected to the action of the pancreatic

juice there were no signs of anaphylaxis. **Nathan** reports a case, the same as one recorded by **Lesné,** in which the patient, a boy of 8 years, always had diarrhœa and an urticarial rash after eating egg. Examination of the stools showed defective functioning of the pancreas, and administration of 40 cg. pancreas daily enabled him to eat eggs with impunity.

Ascoli was able to demonstrate the presence of egg protein in the blood serum of healthy men by means of precipitin tests as early as $1\frac{3}{4}$ hour after the egg was eaten. **Ascoli** and **Vigano** also demonstrated by precipitin tests in dogs that unaltered alien protein, such as egg albumin, appears in the blood soon after it is introduced into the stomach. **Ganghofer** and **Langer** found by precipitin tests that the intestinal tract of young animals permitted the passage of heterologous proteins into the blood serum. Also in 2 debilitated infants they demonstrated undigested egg protein by precipitin tests applied to the blood. **Lust** found that in normal infants undigested egg or beef protein is not absorbed ; but in nutritional disorders he found that egg protein could be demonstrated in the serum and urine by precipitin and anaphylactic tests. **Hayashi** obtained the same results and showed that normal infants do not absorb undigested proteins, whereas infants with nutritional disturbances may do so.

Similar results are recorded also by **Schloss** and **Worten, Hoobler, Talbot, Modigliani,** and **Benini, Lewatschek, Greer, Gruler** and **Bonar.** But **Uffenheimer** and **Hamburger** and **Sperk** could find no evidence of absorption of undigested protein in young animals. As already mentioned earlier, animals can be sensitised by feeding them on foreign proteins as shown by **Wells, Uhlenhuth, Rosenau** and **Anderson, Richet,** and others. **Vauglan, Cummings** and **M'Glumphy** showed that after feeding rabbits on egg protein, their blood was capable of sensitising guinea-pigs to egg protein. **Moro** in 1 case of an atrophic infant found that the blood serum caused complement deviation with milk protein. **Hutinel** records examples of sensitisation passively transmitted through human milk to nursing infants.

From all the above experiments it is clear that, especially in infants with gastro-intestinal disturbances, unaltered proteins may be thrown into the circulation. It has been shown that this unaltered protein produces a group of symptoms, such as vomiting,

diarrhœa, skin rashes, etc., which are probably an expression of anaphylaxis. As sensitisation has been repeatedly produced by feeding animals on foreign proteins, all the evidence goes to support the view that those cases of eczema, where a positive cutaneous test to a food is present and where removal of that food from the diet results in a cure, are due to sensitisation to that food. The cases already referred to, where incomplete digestion of carbohydrates, etc., occurs, can also be explained on the sensitisation theory, because the incomplete digestion leads to absorption in an undigested state and subsequent sensitisation. An eczema due to foods may even occur in infants on the breast. I saw a case recently of a child aged 6 months who had been breast fed since birth. On the mother stopping eating eggs the dermatitis completely disappeared within 10 days. **Talbot** reported a case of very severe eczema in a child which cleared up on the mother's discontinuing the eating of chocolate and recurred on her again eating the food.

Shannon has shown that egg protein may appear in the breast milk after its ingestion by nursing mothers. **O'Keefe** showed that although the infant may give a positive skin reaction to a certain food, the nursing mother does not.

These facts account for the cases of infants who sometimes give positive skin reactions to foods which they have never eaten. If the child is on the breast he may become sensitised to something which the mother has eaten, or if on cow's milk to something on which the cow has been fed, *e.g.* turnips. It also accounts for the cases of children who develop urticaria the first time they are given an egg, and that fact has been quoted as a point against the sensitisation theory.

Although very little is known as to the production of eczema by absorption of proteins other than foods from the bowel, by analogy it may be assumed that in some cases the eczema may be due to sensitisation of the skin to the protein of organisms from the bowel.

Danysz claims that he obtained very good results by treating eczema patients with autogenous vaccines of the organisms grown from the bowel contents. But whether these act specifically or simply as general protein desensitisers is not very clear.

Focal infections have seldom been shown to cause dermatitis.

Morrow described a case of long-standing very itchy eczema of the face and neck which cleared up completely after the removal of teeth which were associated with multiple dental abscesses, and another of generalised erythematous and vesicular eczema in which opening and draining a suppurating joint caused a disappearance of the rash. **Sutton** also, in a discussion on the subject, mentioned a case of vesicular dermatitis of the soles of the feet and another case of dermatitis of the limbs which disappeared when the teeth were put in order.

Whitfield records a case of eczema of the flexural type in a child in whom the disease disappeared after septic tonsils and adenoids were removed.

Cases of definite foci of infection causing eczema, however, seem to be the exception rather than the rule.

There is a good deal of evidence that infections of the lower bowel may cause eczema. In practice, especially in adults, in cases of extensive symmetrical dermatitis where an external cause may be excluded, cutaneous food tests and alterations in the diet may fail to reveal any food as the cause. The only other possibility is some organismal bowel sensitisation, and these are the cases where drinking the waters at a place like Harrogate, and high colon lavage by the Plombière douche give such good results. Every dermatologist has seen cases of this type. I can recall a very marked case in a medical man who had tried all kinds of external applications for years with very little benefit. This patient experienced relief from itching within 24 hours of having the bowel washed out at Harrogate, and a further course of treatment cleared up the dermatitis completely. As soon as the lavage was stopped, within 10 days or so the eruption reappeared. He learned to wash out his own bowel, and found that if he did so once a week his skin remained perfectly well. Cases such as these are undoubtedly due to lower bowel absorption and are probably sensitisations to the organisms growing in the bowel.

When a person becomes sensitised to a food or organism in the intestine, why does the skin cell become sensitised and eczema result ? Why do they not get urticaria or asthma ? No explanation has yet been given, but I would suggest that some trauma, such as rubbing or scratching of the skin whilst the protein is circulating, is necessary. This might break the skin cells and

allow the serum from the blood containing the antigen to sensitise the cells just as occurs in dermatitis venenata. In eczema both the sensitisation of the skin cell and the reaction known as eczema is brought about through the blood stream, whereas in dermatitis venenata these 2 reactions occur from the outside.

THE ASSOCIATION OF ORGANISMS IN THE SKIN WITH DERMATITIS

Numerous attempts have been made to prove that the so-called eczemas are due to organisms. **Unna** is the chief upholder of this theory and some years ago described the " Moro-coccus " which he thought caused eczema. Practically everyone is now agreed that the moro-coccus is the staphylococcus epidermidis albus which is present on every normal skin. This question involves especially the dermatitis known as seborrhœic eczema or dermatitis. In seborrhœa capitis and seborrhœa corporis 3 organisms are now generally admitted always to be present, viz. the seborrhœa bacillus (? acne bacillus), staphylococcus epidermidis albus, and the spore of Malassez. It is still undecided which of these organisms is the causal factor or whether a combination of them is responsible. The same 3 organisms occur in the lesions in seborrhœa corporis or seborrhœic dermatitis. In seborrhœa corporis the lesions start as papular, papulo-vesicular, and vesicular lesions, and end as scaly and crusted areas of a yellowish-red colour, usually spreading peripherally, sometimes clearing up in the centre, and typically seen on the sternal and interscapular regions. There are also the similar inflamed lesions which may occur on the scalp and spread behind the ears on to the neck, in the axillæ, groins, etc. There is no difficulty in assuming the parasitic origin of the more superficial forms of seborrhœa corporis where there are circinate lesions spreading slowly outwards. The ease with which these cases are cured by local applications, the slight degree of itching present, and the gradual slow spread without marked variation from day to day which one sees in other forms of dermatitis, are all in favour of a simple infection with one or all of the seborrhœic organisms. But when larger areas are affected, such as the whole scalp, behind ears, axillæ, groins, and round umbilicus, the condition

does not look quite so like a parasitic one. One must take into consideration the possibility of these cases being sensitisation phenomena. This applies more particularly to the cases where the eruption, although starting on the typical seborrhœic areas, spreads more or less acutely and becomes more or less generalised. The eruption flares up and dies down again repeatedly and is often intensely itchy as in other forms of dermatitis. These cases also are not so amenable to local treatment as the simple circinate cases. Are they cases of sensitisation to some protein by internal absorption in which the seborrhœic virus is implanted on the top, or are they due to the skin or sebaceous glands becoming sensitised to the protein of the seborrhœic virus from the outside ? This difficulty arises particularly in the infantile eczemas which some dermatologists consider as seborrhœic because of the constant implication of the scalp, face, behind ears, flexures, etc. As already mentioned, such cases are often associated with sensitisation to food proteins. If that be so, then the probability is that the lesions are secondarily infected with the seborrhœic virus. By scratching there is no reason why the child should not sensitise himself to the protein of the seborrhœic virus and so produce a double internal and external sensitisation eruption. The same remarks apply equally well to extensive dermatitis in adults, especially in cases affecting chiefly the flexures. The dermatitis may start as a sensitisation to food or bowel organismal protein, and as a result of scratching end as a sensitisation to the skin organisms.

All dermatologists are familiar with the stubborn cases of seborrhœic dermatitis met with during the war. I refer especially to the cases where there was a moist dermatitis of the scalp, eyebrows, and often the beard region, which resisted all local treatment and tended to relapse. Were these cases of sensitisation to the seborrhœic virus or some other organism ? Autogenous staphylococcal vaccines were often very helpful in treatment. That would suggest that these were cases of sensitisation to the staphylococcus which had secondarily infected a seborrhœa.

Medali, in 1915, published the results of treatment of 50 obstinate cases of eczema with autogenous vaccines. The staphylococcus was the most prevalent organism found, but

the streptococcus also was found in a few cases. The results obtained by these vaccines were in a great measure successful.

Strickler, Kolmer, and **Schamberg** did complement-fixation tests with the sera of patients suffering from seborrhœic dermatitis, using the acne bacillus (which some consider as identical with the seborrhœa bacillus), bacillus coli, and staphylococcus. Of the 10 cases of seborrhœic dermatitis which were examined, 30 per cent. reacted positively with the antigen of bacillus acne and 25 per cent. with the staphylococcal antigen. With the antigen of bacillus coli from acne patients, fixation occurred in 40 per cent. of the sera, and in 11 per cent. with the antigen of bacillus coli from normal persons. These results show the presence of antibodies to skin organisms in seborrhœic dermatitis, and support the view that a sensitisation to these bacteria may take place. The percentage of cases which gave a positive reaction to bacillus coli points to the possibility of intestinal absorption playing a part in the sensitisation of the patient.

A local sensitisation of the skin to the seborrhœic infection is another possibility. It is well known that seborrhœic eruptions recur in the same areas of skin each time. It is possible that these areas have become sensitive to the virus, and, therefore, the eruption always recurs in these places.

There is also the type of case of seborrhœic dermatitis of the head and face in adults, in which, quite suddenly, for no apparent reason, the whole face becomes affected with an acute erythematous œdematous dermatitis with swelling of the eyelids, so much so as to suggest erysipelas. Is that an acute streptococcal infection with an organism allied to the erysipelas streptococcus on the top of an ordinary seborrhœic dermatitis, or is it a sensitisation phenomenon? The suddenness with which it comes on, the absence of temperature, and the general appearance of the face suggests a dermatitis venenata. It is possible that the patient is sensitised to the seborrhœic virus and by scratching the skin of the face rubs in the virus, living or dead, and so produces a local dermatitis venenata.

There is another variety of eczema which was first described in 1902 by **Engmann** as "infectious eczematoid dermatitis." This form of dermatitis is frequently preceded by scabies, impetigo, furunculosis, wounds, traumatisms, etc. **Bender, Bockhart,** and

Gerlach showed that it was possible to produce a dermatitis by rubbing filtrates of bouillon cultures of staphylococcus into the skin. **Fordyce,** in 1911, suggested that discharges from ulcers, sinuses, etc., containing the chemical products of the staphylococcus and other organisms, might produce a sensitisation dermatitis.

Bearing on this question also is the observation of **Whitfield,** who noticed, in a case of vesico-bullous eczema of the legs in a gouty individual, that when the bullæ burst and the serum ran down across the legs there appeared in a few minutes a red streak which was followed in about 10 minutes by an urticarial wheal. This was succeeded by a line of vesicles and then a long narrow bulla. When the patient's serum was applied to **Whitfield's** own arm it caused no reaction. **Whitfield** suggests that this patient was sensitised to his own tissue products. Recently **Ferguson Smith** has confirmed **Whitfield's** observation.

Some further observations on the sera of eczema cases have been made. **Bruck** and **Hidaka** studied the cocci found in eczema biologically, but were unable to demonstrate an increase in agglutinins or hæmolysins in the sera.

Kreibich, Brock and **Veillon, Lewandowsky, Dohi, Frédéric** and **Cole** found staphylococci or streptococci, or both, in the vesicles of eczema. But that alone is not sufficient to show whether they were the primary cause of the eczema or only secondary contaminations. **Cole** criticised **Bender, Bockhart,** and **Gerlach's** results in producing a dermatitis by rubbing in staphylococcal filtrates, claiming that the result was due to the alkalinity of the filtrates. He concludes that there is no proof that staphylococcal toxins, as such, produce eczema, although they may play some part in its course. **Coenen** also did some work by rubbing staphylococcal filtrates into the skin, but the lesions produced were pustular and did not resemble eczema. **Rajka** did experiments to see if allergy was present to skin organisms. Autogenous vaccines were made from the skin of each case. The vaccines were exposed to active serum for a time to set free the anaphylatoxin. He used the serum of normal individuals, the serum of eczema cases, and that from blisters of eczema cases. With the vaccines treated with eczema serum he obtained a more marked local reaction by intracutaneous

injection than with vaccines treated with normal serum. Focal, but not general, reactions were found to occur on injection of these vaccines. **Rajka** thinks that the local and focal reactions prove definitely the existence of a skin allergy to pyogenic organisms in eczema.

From all these observations, therefore, there is some evidence, although rather scrappy, that sensitisation to the skin organisms occurs in dermatitis, but there is not sufficient evidence yet to show whether that alone may produce a dermatitis or whether the sensitisation is from other sources and the skin organisms complicate the condition.

Before leaving the subject of dermatitis, it would be well to summarise the results arrived at. Broadly speaking, all cases of dermatitis (including dermatitis venenata, dermatitis seborrhœica, and the so-called eczemas) may be divided into 4 groups :

1. Dermatitis venenata due to sensitisation to plants, chemicals, etc.
2. Dermatitis due to sensitisation to the skin organisms, *e.g.* dermatitis seborrhœica and infectious eczematoid dermatitis.
3. Dermatitis due to food sensitisations.
4. Dermatitis due to sensitisations to organisms in the bowel or some focal infection.

In the first 2 groups the antigen acts on the sensitised skin cell from the outside and in the last 2 from the inside. Assuming that, in all, the skin cell is sensitised, the same mechanism would account for the eruption whether the antigen which provokes it is applied externally or brought to the skin by the blood stream.

CHAPTER XII

DERMATITIS EXFOLIATIVA (Pityriasis Rubra)

Very little is known definitely with regard to the etiology of general exfoliative dermatitis. But since the arseno-benzol preparations have come extensively into use numerous cases of a general red scaly eruption indistinguishable from exfoliative dermatitis have been recorded. Some have ended fatally, others recover completely in 2–3 months if the use of the drug is discontinued. These cases are undoubtedly due to the drug and are to be looked upon as a sensitisation phenomenon. They usually occur after several injections have been given and may or may not be associated with other symptoms. The above cases at once suggest that all cases of exfoliative dermatitis are due to sensitisation to some chemical substance. In exfoliative dermatitis the eruption comes out all over the body and limbs quite suddenly, either in previously healthy individuals or in persons with psoriasis or other eruption. It is well known that over-treatment of psoriasis, especially if it is in an inflamed condition, is apt to bring on an exfoliative dermatitis, which may last for months or years. The cases which occur on the top of psoriasis or seborrhœic dermatitis suggest that it may be due to a special form of sensitisation to the organisms which probably cause these conditions. But in cases where no previous disease has existed, it is possible that the antigen comes from a bowel infection. Foods have never been shown to be associated with exfoliative dermatitis, but chronic rheumatism often accompanies it, and the 2 conditions may have a common origin. Focal infection may in some cases be the cause. **Heimann** reported a case of pityriasis rubra in a man of 60 years of age whose teeth were found to be in a very bad condition. All the

carious stumps were extracted and in 2 weeks the patient was well and has remained so for 3 years.

Pollard described a case with tuberculous glands and lupus vulgaris in which exfoliative dermatitis developed. He considers that in some cases at least the rash is a toxi-tuberculide. Doubtless the cause is not the same in all cases, as drugs and bacterial infections of various organs may produce the same type of eruption just as some of the trichophytides are indistinguishable from tuberculides. A short time ago a female patient was admitted to **Sir Norman Walker's** ward suffering from psoriasis, and whilst in the ward she developed an exfoliative dermatitis all over the body and limbs. It spread, rather slowly for such cases, till the whole skin was affected after 4–5 weeks. Then I gave her 6 injections of sterilised milk intramuscularly, using the milk as a general desensitiser. Within a fortnight the exfoliative dermatitis disappeared, leaving the original psoriasis as before. I have tried the same method in other more old-standing cases but without much result. It is an isolated observation and may have been a coincidence, but I have never seen another case in which exfoliative dermatitis lasted so short a time. Possibly the fact that she was injected so soon after the rash developed had something to do with the result. These cases will be further referred to under non-specific protein therapy.

The fact that the exfoliative dermatitis after drugs like arsphenamin clears up in some weeks after the drug is stopped, and that the so-called idiopathic cases may go on for years, points to the probability that in the latter cases the antigen is still continuously being absorbed, and so the condition is kept up.

Allowing that it is a sensitisation phenomenon, it is a different form of sensitisation from the so-called eczema. Clinically, the eruption is different. It never goes on to vesiculation, and the mechanism of its production must be different from that of dermatitis. Further light is necessary before any more definite opinion can be arrived at.

PSORIASIS

I do not propose to enter into a discussion as to the cause of psoriasis. Personally I hold the view that it is probably an

infection with an organism, and probably spread through the blood stream. No definite organism has been found to be constantly present, but the fact that the spots spread peripherally, healing in the centre, and do not itch much, suggests a simple infection rather than a sensitisation. The fact that it runs in families and only affects certain people suggests that a special condition of the skin is necessary before an individual can be infected. There are also numerous cases recorded, and I have seen 2 cases myself where psoriasis first developed at the seat of a vaccination against smallpox and spread from there to other parts.

Sellei made an extract of psoriasis spots by rubbing up excised psoriasis patches with salt solution so as to produce a milky emulsion. This emulsion was used for injection in doses of 0·1 c.c. and 0·2 c.c. subcutaneously. Eight cases of psoriasis were injected, and in all he noticed a local reaction at the seat of injection. This reaction occurred more quickly and strongly the oftener the injections were repeated at short intervals. Even after quite small injections, in most cases a general reaction with rise of temperature to 38°–38·6° C. followed. In 6 of the cases a fresh psoriasis eruption of small papules, on the top of or around old spots, appeared. This happened in all cases where a general psoriasis was already beginning to disappear. As a control a similar extract of normal human skin was made and similarly injected into psoriasis patients, but without producing either a local or a general reaction. Therefore **Sellei** concludes that in psoriasis there is a sensitisation to the virus.

Stokes tested 3 cases of psoriasis with an emulsion from psoriasis lesions. He obtained a local reaction with this emulsion by the intradermal method only and not by the Pirquet method.

Further confirmation of these results is, however, necessary.

I have tried to desensitise psoriasis cases with peptone and milk injections. Many others have also tried vaccines and various protein desensitisers, but, as will be seen later when desensitisation is discussed, the results have not been very encouraging. If psoriasis is due to an infection with an organism it cannot be one which produces any virulent toxin, as the general health is often quite good and there is no rise of temperature. Therefore, if patients are sensitised to psoriasis, they seem to

remain in the sensitive stage and do not go on to immunity. That would account for the cases always relapsing after apparent cure. From the way in which the eruption in the average case slowly spreads, not flaring up and dying down as in dermatitis, I am inclined to think that patients with psoriasis are not highly sensitised to the infection.

ACNE VULGARIS

It is now generally accepted that acne vulgaris is due to the acne bacillus. The simple infection of the sebaceous gland follicles leads to the comedo, but when the infection goes deep into the corium the large swollen lesion results. This lesion microscopically is a granuloma with giant cells. These lesions resemble structurally tubercle and tertiary syphilis, in both of which cases a bacterial sensitisation is present. The more highly the patient is sensitised, probably the larger the lumpy lesions are. An acne, if left untreated, remains for some years in this sensitive stage, lesions coming and going till it goes on to complete immunity and the disease dies out. No cutaneous tests have been done in these cases with acne cultures, but vaccines are often very beneficial in treatment.

Complement-fixation tests were done by **Strickler, Kolmer,** and **Schamberg.** Fifty-seven cases were tested, and well-marked positive reactions were obtained to the antigen of bacillus acne in 84·2 per cent. of the cases. As a rule, the more severe the infection the higher were the percentages and degree of complement-fixation. With the antigen of staphylococci from acne cases positive reactions were found in 64 per cent. Similar results were also obtained using the antigen of staphylococci from boils. This indicates that the staphylococcus found in acne does not differ from the ordinary staphylococcus of furuncles and other lesions and is probably a secondary infection. With a polyvalent antigen of bacillus coli from the intestine of acne cases positive reactions were obtained in 63·1 per cent. of the cases, and the control antigen of bacillus coli from other sources only yielded 32 per cent. positive reactions. This would indicate that the colon bacillus may have something to do with the pathogenesis of acne. Complement-fixation tests, using acne,

staphylococcal, and bacillus coli antigens in syphilitics with positive Wassermanns and in other chronic diseases, in 26 patients were uniformly negative. These results show therefore that in acne vulgaris there is a sensitisation to the acne bacillus and also to the staphylococcus and bacillus coli. The character of the lesion and the results of vaccine treatment also support the sensitisation theory.

STAPHYLOCOCCAL INFECTIONS

These include Bockhart's impetigo, furunculosis, and sycosis.

In Bockhart's impetigo and furunculosis there is evidence that in some cases at least the patient becomes sensitised and remains for some time in that state. In most cases the disease is either cured by local treatment and removal of the virus or, after a number of lesions have been produced, desensitisation or immunity results. Vaccines are well known to be beneficial in furunculosis, but whether a true sensitisation occurs in these cases there is no evidence to show. Possibly it does occur in these bad cases of multiple boils which are so difficult to treat, and in cases which have been over-vaccinated.

Sycosis is definitely a staphylococcal infection of the hair follicles. Here again vaccines are beneficial. These cases may go on for years and the whole affected area become red and moist like a dermatitis. Sycosis suggests a sensitisation to the staphylococcus. If it is, it is probably local and not general. **Besredka** from experiments on animals concludes that staphylococcal vaccination depends on the production of a local immunity of the skin. He got better results by applying the vaccine cutaneously than by injecting intra- or sub-cutaneously.

Altmann and **Bluhdorn** obtained positive complement-fixation tests in staphylococcal infections in animals.

Schreus and **Goehl** in 2 cases of pyodermia found marked positive complement-fixation with staphylococcal vaccine.

Ledermann and **Wassermann** worked with a preparation called Histopin which is an immunising fluid made by shaking living staphylococci for a long time in water. This extract was made into an ointment in strengths of 25–50 per cent. and applied to staphylococcal impetigos, boils, etc. They found that the development of fresh lesions could be prevented and

existing lesions healed rapidly. They think that the histopin influences the local immunity. **Beck** confirmed these results to some extent, but found that in furunculosis, sycosis, and staphylococcal folliculitis the results were not uniform. The best results were obtained in superficial lesions. Occasionally **Beck** observed a local reaction around the area where the histopin was applied.

Astonishingly little work has been done on the question of sensitisation to the staphylococcus considering how frequently it complicates skin conditions, but what evidence there is points to a low degree of sensitisation of the skin which in some cases, as in sycosis, is probably local and not general.

SKIN ERUPTIONS IN GONORRHŒAL INFECTIONS

According to **Buschke** the usual skin complications of gonorrhœa are :

1. Scarlatiniform erythema.
2. Urticarial rashes.
3. Bullous and hæmorrhagic rashes.
4. Rashes resembling erythema multiforme.
5. Lesions like erythema nodosum.

He thinks that the eruption is partly due to circulating gonococci and partly to toxins. In some of the nodular rashes the lesions suppurated and the gonococcus was obtained from them. All the above rashes are of the type which we have already seen to be hypersensitive phenomena. **Hodara** and others have demonstrated the gonococcus in the blood in such cases, and it is probable that the individual is sensitised to the gonococcus and the rash results from the reaction between the sensitised skin and the organism brought to the skin by the circulation.

There is also the rare condition known as keratodermia blenorrhagica which most commonly affects the feet, but may appear elsewhere. The lesions begin as vesicles and soon become pustules whose wall becomes keratinised, forming round hard lesions. Opinion is divided as to whether this eruption is due to the presence of the gonococcus or to toxins acting directly on the skin or through the nervous system (tropho-neurosis). **Lees** considers it to be a toxic local manifestation of the general systemic

infection, as shown by the accompanying cachexia, muscle wasting, and anæmia. **Jacquet, Chauffard**, and **Fiessinger** succeeded in reproducing the lesion in a patient by inoculating the skin under a watch-glass with serum from a keratotic lesion. **M'Donagh** found a lymphocytosis of the cerebro-spinal fluid and considers the eruption to be due to meningeal irritation of the trophic fibres of the posterior nerve roots caused by the gonococcal toxins. The gonococcus has frequently been found in the blood, but only once in the lesions in these cases. It may, however, be a sensitisation rash similar to the others which occur in gonorrhœa, but with the addition of possibly staphylococcus or other organism which causes the curious keratotic growths.

CUTANEOUS TESTS IN GONORRHŒA

Numerous workers have performed cutaneous tests with gonococcal vaccines and toxins. **Bruck, Eisig, Giorgis, Irons, Kohler, London, Fuchs, Finkelstein** and **Gerschun,** and **Decastro** all obtained positive reactions in the majority of cases. **Sakaguchi** and **Watabiki, Brandweiner** and **Hoch, Simon** and **Somner** found positive reactions in only a small percentage of cases. The cutaneous and intracutaneous methods were used. Some observers obtained positive reactions in control cases, but these were not very numerous. **Fuchs,** using **Neisser's** gonococcal vaccine (gonococcal broth) for intradermic tests, found that, as a rule, the reaction appeared about 6 days after the disease developed, and that it was present for some months after the disease was healed. The reaction was not associated with any special clinical form of gonorrhœa. Treatment with gonococcal vaccine did not produce any change in the reaction. **Fuchs** considers that the test can be used to determine whether a case is definitely cured.

Positive complement-fixation reactions have also been shown to occur in gonorrhœa, especially in general infections, and treatment with vaccines has been very successful, especially in the complications of the disease. Focal and general reactions also occur in gonorrhœal infections after intravenous or intramuscular injection of gonococcal vaccine.

From the above facts I think we are safe to conclude that the gonococcus is capable of producing a true bacterial sensitisation.

CHAPTER XIII

FOCAL INFECTION

The term focal infection is rather a wide one. It includes the local effect of the invasion of an organ with organisms and the spread of the infection from the primary focus by lymphatics or blood stream to other organs, there to produce similar lesions. But the term is also used to designate the changes which take place in organs at a distance from the primary focus, due to the absorption of toxins or other chemical substances from that focus. In diseases such as syphilis and tubercle we have seen that various skin rashes are produced by the organisms, which come by the circulation from a focus or foci, reacting on the sensitised skin, and in a sense these diseases are focal infection diseases; but under this section will be discussed a series of diseases of the skin which are probably due to the action on a sensitised skin of various toxic substances absorbed from a focus of infection. The possible sources of absorption are the gums in pyorrhœa, teeth in apical abscess, tonsils, lymph glands of naso-pharynx, neck, mediastinum, abdomen, etc., mastoid, maxillary antrum, and other accessory sinuses, bronchi, endocardium, gastro-intestinal tract, appendix, gall bladder, genito-urinary tract such as kidney, bladder, prostate, seminal vesicles, uterus, or Fallopian tubes. Infected lymphatic glands are secondary to the primary focus, and secondary foci in the glands, etc., may persist long after the primary focus has healed. The organism most commonly associated with these focal infections is the streptococcus. The flora of the mouth, teeth, and tonsils include chiefly the hæmolytic and non-hæmolytic streptococci and the staphylococcus. **Sir William Willcox**, writing on infections of the teeth and gums, refers especially to the hæmolytic group of streptococci which cause severe toxæmias and rashes of various kinds, especially the purpuras. The organism may grow

in an organ such as the tonsil and produce very little local effect, but the breaking down of the organism by ferments or other means leads to the production of toxic substances which may act on the sensitised skin.

The tissues which are most often associated with focal infections are the teeth and gums, naso-pharynx, tonsils, and the lymphatic glands connected with these tissues. In many cases there is obvious pyorrhœa alveolaris, or carious teeth are present. In these cases there is no difficulty in the diagnosis, but there may be abscesses at the root of the teeth which cause no symptoms, and in such cases an X-ray photograph of the teeth is necessary to demonstrate the lesion. The fact that a patient has no visible teeth does not necessarily exclude that source of infection, as infected stumps from previous imperfect extractions may be present and can only be revealed by X-rays. It is also very difficult to tell by looking at a tonsil whether it is the seat of an infection. Many small tonsils with old fibrosis and pockets of pus are less conspicuous than the large tonsil with wide crypts but no deep infection. The removal of a septic focus in the jaw or tonsil may lead to a temporary aggravation of the associated skin condition by opening up the lesion and causing a fresh absorption. The fact that the lymphatic glands may be the seat of secondary foci also makes treatment more difficult, as the symptoms may persist after the primary focus is removed. Infections of teeth, gums, and tonsils are so common that, as **Ravitch** and **Steinberg** pointed out, " we must be careful not to accept a certain number of coincidental cases as proof." Out of 100 cases of skin diseases with focal infections, **Sutton** found that 75 per cent. improved markedly or recovered after finding the focus and removing it. In the other 25 per cent. he was unable to find any direct relation between the focal infection and the skin disease.

The question of focal infection has already been referred to under Urticaria, Erythemata, Eczema, Purpura, Dermatitis Herpetiformis, and Exfoliative Dermatitis, but in these diseases a focal infection is only one of many sources from which the eruption may originate. There is still a group of diseases in which it is probable that the skin rash is always due to absorption of toxic substances from a focal infection. Into this group fall lupus erythematosus, alopecia areata, prurigo, and possibly also

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pruritus ani and vulvæ and generalised pruritus. Herpes zoster has been mentioned by several writers as an example of focal infection. In the sense that there is a focus of inflammatory infection in the ganglia, producing a skin eruption in the distribution of the sensory nerves associated with these ganglionic cells, herpes zoster might be called a focal infection, but in these cases there is no sensitisation of the skin, and therefore herpes zoster does not come into the group which we are discussing.

Scleroderma and vitiligo have also been mentioned by **Chipman** and others as possibly associated with focal infection, but very little indeed is known of the etiology of these diseases. Recent work rather points to some endocrine gland change in scleroderma, but whether the gland change is due to absorption of toxins from some focus is not yet decided. Similarly, vitiligo may have some association with a toxic nerve lesion. Further information on these diseases is necessary before they can be elucidated.

LUPUS ERYTHEMATOSUS

Barber, in 1915, published a severe case of lupus erythematosus of the face, neck, ears, scalp, hands, and left elbow, in which plates prepared from her fæces gave a practically pure culture of a streptococcus longus. She developed later what was apparently a streptococcal septicæmia with high fever and rigors, and the rash spread over the back. She was extremely ill for some days, after which the temperature gradually fell to normal and the rash all disappeared except a few of the older patches on her face. At this stage no streptococci were to be found in her fæces. No blood culture was taken during the febrile stage, but **Barber** came to the conclusion that the eruption of lupus erythematosus was due to absorption from the streptococcal focus in the intestines, and the fever to a general infection of the circulation with the streptococci. During the febrile attack sufficient antibodies had been formed to destroy the streptococci in the blood and intestines.

In 1919 **Barber** reported another case of lupus erythematosus of discoid type on the face, ears, and scalp. In this case examination of the fæces failed to show any streptococcus longus. The tonsils were considerably enlarged and appeared septic, and the

glands at the angle of the jaw were enlarged. A swab from a tonsillar crypt gave a pure growth of streptococcus longus. The tonsils were removed and the operation was followed by a rise of temperature to 99·6° F. An autogenous vaccine was made and a dose of 5 millions given the day after the operation. This caused a definite focal reaction in the patches of lupus erythematosus, which swelled up, became very irritable, and showed signs of spreading. This reaction lasted about 24 hours. Two days later another similar dose was given and the temperature rose to 99·8°, and again a focal reaction occurred. Eight days later 10 millions of vaccine were given, and that produced considerable constitutional reaction, with a temperature and an intense focal reaction in the skin lesions which became congested and spread considerably. An old healed lesion flared up again also. The pyrexia lasted some days and gradually subsided, and the patches showed signs of healing; but an acute attack of inflammation in the remaining lymphoid tissue of the throat was immediately followed by a very severe focal reaction in the skin lesions. The complete removal of all the infected lymphoid tissue and the use of a sensitised vaccine caused all the lesions to retrogress completely. **Barber** also mentions another case of lupus erythematosus on face and hands, with infected tonsils. Their removal caused a febrile attack of several days' duration and a focal reaction in the skin patches. An autogenous streptococcal vaccine was made from the tonsils, and when it was given the skin lesions entirely disappeared.

Since **Barber's** cases were published several other observers have recorded similar results. **Whitfield** reports cases of lupus erythematosus where treatment for pyorrhœa caused the eruption to disappear, and others where enucleation of the tonsils and the administration of an autogenous vaccine produced the same result. **Leslie Roberts** also reports improvement in a case of lupus erythematosus after tonsillectomy. **Hartzell** recorded a case where removal of a "capped" tooth with an abscess at the root caused marked improvement in a lupus erythematosus, although much previous local treatment had had very little effect.

In 1920, along with **Logan** and **Rutherford,** I published the post-mortem report of a case of generalised lupus erythematosus. This case was first seen in 1915 with an acute lupus erythematosus

of face, ears, and left hand, accompanied by pyrexia (100° F.) which subsided under treatment with quinine and rest in bed. The eruption persisted for 2 years on face and hands as a lupus erythematosus of discoid type. Then it entirely disappeared for nearly a year. In 1918 she had another acute attack in which the eruption reappeared on face, ears, neck, hands and forearms, and thighs, and the temperature ran between 100° and 103° F. The patient became extremely ill and emaciated after the temperature and rash had continued for 3 months. Then the temperature gradually fell and the rash disappeared entirely. But 17 months later she had another recurrence of the temperature and rash, the latter being even more extensive than previously. She died after this attack had lasted about 2 months. Cultures from the heart-blood post-mortem yielded a pure growth of streptococcus longus. Unfortunately the case was complicated by the finding of an unsuspected laryngeal diphtheria. It could not be decided whether the streptococcus had gained access to the blood shortly before death as the result of the diphtheria, or whether it was there previous to that. The fact that a blood culture made a month before death was negative cannot be held as conclusive that no organisms were present at that time. There was also a subacute pericarditis evidently not tuberculous, and it is possible that the pericardial lesion was the focus from which the streptococci arose. A vaccine was made from the streptococcus obtained from the above patient's blood and used to treat another case of lupus erythematosus of face, scalp, and hands in a girl aged 14 years. This case had apparently no tonsillar lesion. Several bad teeth were removed and then the vaccine treatment was commenced. As she improved markedly, the treatment was continued, after the special vaccine was finished, with a stock polyvalent streptococcal vaccine. She was given an injection once a week beginning with 5 millions and gradually increasing up to 150 millions. The treatment extended over nearly 9 months, and at the end of that time nearly all the eruption had disappeared. A month after the vaccine was stopped there was a recrudescence of the eruption on several of the old areas. The presence of an enlarged tender gland under the right side of the lower jaw suggested that there was still some undiscovered focus in the mouth or throat. The vaccine

was resumed, and has been continued weekly till now. She has again improved, but evidently the vaccine is not capable of causing a complete cure.

Another case of lupus erythematosus of left cheek and scalp, Mrs. K., age 38, was treated with an autogenous vaccine of streptococcus longus obtained from an inflamed right tonsil. At the end of 5 months the face lesion has entirely healed and the scalp lesion is much better.

A third case of lupus erythematosus, Mrs. H., aged 42, was treated with streptococcal vaccine. No focal infection could be found in the throat and all her teeth had already been removed. After 3 months' streptococcal vaccine treatment the eruption entirely disappeared, but 6 months later there was a slight recurrence of eruption. After one of the vaccine injections she showed a focal reaction in the skin lesion similar to that recorded by **Barber** in his cases.

In 1920, with **Rutherford**, I published a case of lupus erythematosus in a woman aged 56 years, affecting the face and ears. She had bronchitis, with streptococcus longus and Friedländer's pneumo-bacillus present in the sputum. Her teeth were extremely bad and the upper and lower gums showed marked pyorrhœa. All the bad teeth were extracted and she was given a vaccine of pneumo-bacillus and streptococcus longus made from the sputum. The bronchitis soon subsided and the lupus erythematosus improved greatly, healing completely in several areas. Three months later she had another attack of bronchitis, with staphylococcus aureus and streptococcus longus in the sputum. At the same time the lupus erythematosus relapsed and she showed an eruption very similar to what she exhibited on the first attack. She died of heart failure and bronchitis a month later. As the post-mortem examination was not made till 24 hours after death no cultures were made from the blood or internal organs, but a very thorough search of all the organs, both naked eye and microscopically, failed to reveal any trace of tuberculosis. I do not propose to enter into a discussion as to whether lupus erythematosus is a form of tuberculosis or not, but even 1 case where tubercle could be absolutely excluded is, I think, sufficient proof that tubercle is not the cause of the condition. The appearance of the rash, both naked eye and micro-

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scopically, is against tuberculosis. On the other hand, **Barber's** suggestion that it is due to the absorption of some substance produced in a focus of streptococcal infection acting on a sensitised skin gives a much better explanation of the condition than any other. It has long been recognised that the eruption of lupus erythematosus is closely related to the erythemata which we have seen may be caused by focal infection. The good results obtained by removal of infected tonsils and of sepsis of the teeth and gums, and by the use of an autogenous vaccine, also support this contention. Therefore, in the ordinary cases of lupus erythematosus of face and ears, etc., the probability is that a streptococcal focus in teeth, gums, adenoids, tonsils, bowel, or bronchi is the cause of the condition. There is some evidence also that exposure to light has something to do with the localisation of the eruption on the nose, cheeks, ears, and hands, which are the common situations for it. **Barber** mentions a case of **Sequeira's** where lupus erythematosus appeared after the application of Finsen light and poultices. Sunburn has also been held responsible for its appearance in some cases.

In the cases of generalised lupus erythematosus, as **Barber** suggested, there is probably, in addition to the original focus, a blood infection with the streptococcus. The streptococcus circulating reacts with the skin cell to produce the rash. As **Barber's** and my cases show, the patient may become desensitised and recover both from the septicæmia and the focal infection. The generalised cases resemble very closely malignant streptococcal endocarditis both, clinically, in the way the temperature remains persistently high and in the fact that there is a focus of infection in the heart valves from which streptococci are shed into the circulation. In malignant endocarditis there is probably no sensitisation of the skin, and therefore no rash occurs.

ALOPECIA AREATA

The true nature of alopecia areata is still in doubt. Three theories have been supported by different sets of observers :

1. Microbic.
2. Nervous.
3. Toxic.

1. *Microbic Theory.*—This theory was strongly supported by **Sabouraud** and others. The seborrhœa bacillus, spores of Malassez, staphylococcus epidermidis albus have all been held responsible. If organismal, it should be transmissible, but the experiments of **Jacquet** and others on man and animals have all been negative. The fact that epidemics have been described does not necessarily support this theory, as a toxin in food might explain epidemics in institutions.

2. *Nervous Theory.*—This theory probably has the most support from dermatologists at present. It is well known that the disease may follow mental strain and shock. Local injuries may also cause it. I have seen a patch of typical alopecia areata develop on the side of the head following a severe smash which resulted in fracture of the zygomatic arch and severe contusion. In this case the patch was rounded and showed typical exclamation-mark hairs at the margins. This case could be explained on the assumption of a traumatic neuritis. The fact that alopecia areata spreads at the edges is not necessarily proof of its parasitic origin, as the trophic nerve to a given area might be affected, and as the neuritis spreads up the nerve it implicates the smaller branches which come off further up, and so as the neuritis spreads up the nerve the spot of alopecia enlarges at the edges (Plate facing p. 176). **Jacquet's** theory that it is due to reflex irritation from carious teeth had some supporters, but as will be seen later there is another explanation of how the teeth may cause the condition. **Whitfield's** cases, where removal of eyestrain cured the alopecia, also support the nervous theory.

3. *Toxic Theory.*—This theory is chiefly supported by the fact that injection of various bacterial toxins into the skin of animals has often resulted in bald patches. Staphylococcal pustules on the scalp as a rule cause the hair to fall out in these areas, presumably from the effect of local toxins. Acetate of thallium, if taken internally, will also cause the hair to fall out, but as it is a nerve poison the effect of this drug rather supports the nervous theory.

Each of the above theories has something to recommend it in given cases, but none of them seems to explain all cases. Since attention has been drawn to the effects of focal infection, such an infection has been suggested as the cause. This theory fits in

with the nervous and toxic theories, because a toxin absorbed from a focal infection may act on the trophic nerves to the scalp and so produce the lesion. **Chipman,** in 1917, reported focal infections of teeth in cases of alopecia areata. In 1921 **Barber** and **Zamora** published some very suggestive cases where removal of septic foci, containing the streptococcus longus, in teeth, gums, tonsils, or naso-pharynx, and the administration of an autogenous vaccine, led to recovery or marked improvement in the alopecia areata. In their series of 9 cases, they found infected tonsils with or without adenoids in 62 per cent., oral sepsis alone in 5 per cent., oral and tonsillar sepsis in 25 per cent., chronic otitis media and naso-pharyngitis in 2 per cent., chronic naso-pharyngeal catarrh in 4 per cent., and severe ethmoidal suppuration in 2 per cent. In 11 cases of alopecia areata **Leslie Roberts** found evidence of bacterial collections in the tonsillar crypts in 5 cases, the other 6 showing no evidence of tonsillar infection. Of the 5 with cryptic collections 3 had tonsillectomy performed, with good result in 2 of the cases. Of course, as **Barber** and **Zamora** point out, one must be careful in drawing conclusions in a disease such as alopecia areata, which runs such an indefinite course. Because the hair grows in again after a certain form of treatment, that is no proof that it was " propter hoc " and not " post hoc." In all cases of alopecia areata I now look for focal infections in teeth, tonsils, etc., but in cases where visible foci have been removed I cannot say that the results have been very startling. However, the theory that a toxin is absorbed from some focal infection and acts on the sensitised nerves to the scalp, resulting in the fall of the hair, has much to recommend it, and time and careful observation in a large series of cases should enable us to prove or disprove it.

LICHEN PLANUS

As in alopecia areata, the microbic, nervous, and toxic theories have had their supporters from time to time; although no microbe has been found, the supporters of this theory base their belief on the fact that the eruption often occurs in the line of scratch marks, suggesting a local inoculation. Arsenic, antimony, and mercury, all drugs which are useful in syphilis,

are also useful in lichen planus. Sudden shock, worry, and anxiety also frequently precede the eruption. The severe itching also suggests the implication of the nervous system, and **Thibièrge** and **Ravaut** and **Pernet** report the marked effect of lumbar puncture on the itching. The eruption in some cases appears to follow the line of nerve distribution. In the acute cases the sudden appearance of the eruption like an exanthem has been held to support the toxic theory, but it also supports a microbic cause.

In a discussion on focal infection in 1917, **Sutton** mentioned a case of lichen planus in which removal of several apical abscesses in teeth was followed by a cure. **Chipman** also states that lichen planus is frequently associated with dental abscesses, but **Whitfield** cannot corroborate this. **Leslie Roberts** also records a case of lichen planus with marked pyorrhœa in which removal of all the teeth resulted in the eruption completely disappearing about 20 days later. The material on which to form an opinion is still too meagre, and, as in alopecia areata so in lichen planus, more evidence is necessary before it can be determined whether or not focal infection is the causative factor.

PRURIGO (OF HEBRA)

Prurigo is a disease which suggests a sensitisation phenomenon. It begins with an eruption like urticaria papulosa, and continues more or less all the life of the patient. Eosinophilia in the blood is also quite regularly present. Alternating attacks of asthma may also occur with prurigo, and I think that practically all the so-called eczemas alternating with asthma are really cases of prurigo.

In 4 cases of prurigo in which I did cutaneous tests to all the common foods, 3 were absolutely negative, but 1 gave positive reactions to egg white, egg yolk, and cod-fish. Removal of these articles from the diet caused no improvement in the eruption, and feeding the patient on them did not aggravate the condition. These cases will be referred to again later in discussing cutaneous food tests. **Schwartz** thinks that in prurigo there is evidence of protein putrefaction as shown by the presence of indicanuria, and states that attacks of eruption follow a high

protein intake. As sensitisation may be produced by the alimentary route by overfeeding with protein, **Schwartz** thinks that food protein plays an important part in the production of prurigo.

The disease in sheep known as "scrapie" is somewhat like prurigo. The animals rub and scrape themselves, especially on head, neck, and limbs, producing thickening of the skin and enlarged glands as in prurigo. **M'Gowan** showed that scrapie is due to a sarcosporidium encysted in the muscles of the limbs near their insertions into bone. The toxin circulating seems to cause the skin itching. In a case of prurigo Mr. D. P. D. Wilkie kindly removed a piece of muscle from the elbow region for me, but no sign of sarcosporidium was found.

Leslie Roberts reports a case of long-standing prurigo who had septic collections in the crypts of the tonsils. Tonsillectomy, followed by the administration of an autogenous vaccine of staphylococcal aureus and streptococcus longus, caused an extraordinarily rapid improvement in the skin condition, so that in 3 months the case was practically cured.

In 1920, from a typical case of prurigo of 11 years' duration in a boy aged 14 years, under **Sir Norman Walker's** care, enlarged tonsils and adenoids were removed, but with no result on the eruption, and now (1923) his skin is in much the same condition as previously. Some other focus which was not detectable may, however, have been present.

Prurigo suggests the circulation of some toxin acting on a sensitised skin. **Leslie Roberts** succeeded in removing the focus of infection in his case, but the tonsil is evidently not the only possible source of toxin. Further investigation of these cases on the theory of focal infection will probably disclose its true nature.

PRURITUS ANI AND VULVÆ AND GENERALISED PRURITUS

It is a question whether pruritus, general or local, should be included under focal infections. There is no direct evidence for or against it, but it is known that in certain blood diseases such as leucæmia, in toxæmias like diabetes, gout, rheumatism, etc.,

severe itching may occur. Certain foods produce itching on some individuals, such as shell-fish, mustard, coffee, etc. Jaundice is also another well-known cause. These are probably examples of toxins, using the word in its widest sense, irritating the nerve-endings in the skin and so causing itching. As the itching only occurs in certain individuals it suggests that there is some change in the nerves possibly of the nature of a sensitisation. In dermatitis venenata, where the skin is sensitised, itching is one of the most prominent features. Many cases of generalised pruritus occur in elderly persons with arterio-sclerosis, which would suggest that the same toxæmia which caused the arterio-sclerosis also causes the pruritus. I have seen several cases markedly benefited by a course of internal treatment at Harrogate. In the local forms (pruritus ani and vulvæ), it has been suggested that the lesion is due to an infection with an organism in that region. **Murray** in 19 cases of pruritus ani found the streptococcus in the skin in all cases, and **Winfield** in 50 cases found streptococcus and bacillus coli alone or mixed in 40 of them. Both observers obtained remarkably successful results with autogenous vaccines. It is possible that in these cases a local toxin is produced to which the nerve-endings become sensitised.

CHAPTER XIV

SENSITIVENESS OF THE SKIN TO LIGHT

THERE are two diseases in which the eruption is due to the effect of the actinic rays of light, viz. :

(1) Hydroa vacciniforme or æstivale ; and
(2) Pellagra.

HYDROA VACCINIFORME OR HYDROA ÆSTIVALE

Under this head we do not include the ordinary dermatitis solare seen normally from exposure to strong sunlight. This dermatitis is followed by a protective pigmentation of the skin. Nor does it include the chronic atrophic condition of the skin, with frecklelike pigmentation and atrophy, seen in white persons who are exposed for years to strong sunlight such as occurs in the Tropics.

Hydroa æstivale occurs in two forms. The severe form shows vesicles and bullæ on face, ears, and hands on exposure to the light. From their appearance **Bazin** named the disease hydroa vacciniforme. The lesions leave scars which may contract later and cause deformities.

The mild form of the disease was described first by **Sir Jonathan Hutchinson** under the name of summer prurigo. The lesions consist of small papules resembling those in a papular dermatitis. Both forms usually begin in childhood and recur every summer till adult life, when it tends to disappear. Cases have been recorded, and I have myself seen one, which did not develop till adult life. The eruption is due to the actinic rays of the light, as can be demonstrated by exposing the skin to sunlight or artificially produced ultra-violet rays.

One of the most recent articles on the subject is by **Senear**

and **Fink,** who review all the 80 hitherto published cases. Males are more often affected than females in the proportion of 2 to 1. Hæmatoporphyrinuria occurs in a certain number of cases. **Senear** and **Fink** state that in all the 80 published cases it was only present in 17·5 per cent. of them. But as it may only be present temporarily or in other forms, it is probably a much more constant factor than those figures indicate.

Some 2 years ago, when going through the literature on urticaria and its relation to sensitisation, I came across an article by **H. L. Smith** in which he reported a case of urticaria, angio-neurotic œdema, and vomiting in a boy whenever he ate buck-wheat. He gave a local cutaneous reaction to buckwheat grain applied to a scarified area. In this article **Smith** refers to buckwheat poisoning, or fagopyrismus, which occurs in white or white-spotted animals that have been fed on common buck-wheat (*Fagopyrum esculentum*). The disease is commonest in swine and sheep, but occurs occasionally in cattle and goats and very rarely in the horse. Clinically, the milder form of the disease is associated with an itching erythema, chiefly of head and face, constipation, and digestive disturbances. The more serious cases show a vesicular, pustular, or gangrenous dermatitis with fever or urinary phenomena. White or spotted animals are said to be exclusively affected. Those that are black or artificially blackened escape the disease, and in black and white animals only the white parts are affected by the dermatitis, the black areas remaining quite normal. The worst cases of buckwheat poisoning are seen in animals that have been fed on the buck-wheat plant when in bloom, but the disease may develop after eating the grains, bran, chaff, straw, or stubble. Sunlight is the exciting cause. If the animals fed on buckwheat are kept under shelter or allowed out under cloudy skies they seldom develop the disease, and, if they do, only in the mild form. But if the animal is put out in a strong sun it rapidly develops the symptoms, including the dermatitis on the white parts of the skin only. The interesting fact of this disease is that buckwheat contains phyloporphyrin, a derivate of chlorophyl, which closely resembles, chemically, hæmatoporphyrin and mesoporphyrin. It shows an almost identical absorption spectrum with these two hæmatin derivatives. When phyloporphyrin and hæmatin

are reduced by concentrated hydrochloric acid they both yield hæmopyrrol, and hæmopyrrol is converted into hydrobilirubin by the action of sunlight.

It is obvious that these facts throw some light on the causation of hydroa vacciniforme in which hæmatoporphyrin occurs in the urine and presumably in the blood. **Ehrmann**, in 1909, seems to have been the first to suggest that hæmatoporphyrin in hydroa vacciniforme acts as a sensitising substance and is the cause of the skin eruptions. **Sachs** and **Sacharoff** had previously found that red-blood corpuscles in solutions of photodynamic substances were rapidly hæmolysed, whilst control suspensions kept in the dark remained unchanged. **Pfeiffer** confirmed this observation. **Hausmann** had also previously shown that, under the influence of light, rapid hæmolysis occurs when the extracts of chlorophyl plants are added to red-blood corpuscles, but when kept in the dark no hæmolysis takes place. He also found that hæmolysis results when bile is allowed to act on red-blood corpuscles in the presence of light, and hæmatoporphyrin has even greater sensitising properties than bile when activated by light. **Hausmann** also injected white mice with pure hydrochloride of hæmatoporphyrin, and found that, on exposure to sunlight, they scratched themselves, their skin became red and œdematous; they became restless and in some cases died. Therefore in fagopyrismus the phyloporphyrin, and in hydroa vacciniforme the hæmatoporphyrin, circulating in the blood acts as a sensitiser, like photodynamic substances, when exposed to sunlight.

A good deal of work has been done on photodynamic substances. **Tappeiner** showed that acridin hydrochloride, which is a substance which shows marked fluorescence, in the presence of daylight is able to kill infusoria, whereas in the dark it is absolutely harmless. The same results were obtained with other fluorescent substances. **Tappeiner** called these substances "photodynamic sensitisers." **Herxheimer** and **Nathan** group eosin, erythrosin, carboneol (tar preparations), and other fluorescent substances together with hæmatoporphyrin as photodynamic substances. Painting the skin with these substances has been used to increase the effect of light in the treatment of skin diseases where a marked reaction was desired.

Sobernheim, in 1892, showed that after prolonged administration of sulphonal in man hæmatoporphyrinuria appeared, and **Neubauer** also demonstrated the same fact in rabbits.

Perutz, in 1917, fed a rabbit on increasing doses of sulphonal till hæmatoporphyrin appeared in the urine, and then exposed its ear to the Kromayer lamp for 3 minutes only. This resulted in redness, swelling, and blistering of the skin, whilst control animals showed absolutely no reaction at all. This experiment was repeated several times and always with the same result. The reaction areas crusted over and healed with scars. **Perutz** fed the same animal again on sulphonal till hæmatoporphyrin appeared in the urine, and then exposed the ear scarred from a previous reaction and also the other ear to the Kromayer lamp, and obtained a reaction on the second ear but not on the scarred one. This is explained by the absence of circulation in the skin of the scar. **Gotzl** also found that by injecting lead triathyl he could produce hæmatoporphyrinuria in animals, and these animals were very sensitive when exposed to ultra-violet rays. **Meyerbetz** experimented on himself. As hæmatoporphyrin is not absorbed when taken by the mouth, he injected 0·2 cc. hæmatoporphyrin intravenously into himself and then exposed an area of skin on his right arm to the Finsen light. This produced a reaction which resulted in hæmorrhage into and sloughing of the skin, which only healed with scarring after several weeks. On the day after the injection he exposed himself for a short time to the sun, which caused œdema and redness of hands and face which lasted several days and left marked pigmentation.

Hæmatoporphyrinuria is a symptom of liver-insufficiency. Under certain conditions a reduction product of hæmatoporphyrin called mesoporphyrin may appear. Mesoporphyrin has nearly the same spectrum absorption bands as hæmatoporphyrin, and **Fischer** thinks the two substances should be combined under the one name Porphyrine. **Fischer, Bartholomaus,** and **Rose** succeeded in finding the mother substance of porphyrin. They called it porphyrinogen. By oxidation porphyrinogen becomes mesoporphyrin. It is known that in many cases of hydroa vacciniforme and æstivale the hæmatoporphyrin was only present in the urine at certain times, but **Perutz** showed that if one oxidises the urine with potassium permanganate, it gives

the spectrum of hæmatoporphyrin, showing that the urine has porphyrinogen in it. Porphyrinogen is colourless, and, therefore, in all suspected cases of light dermatitis the urine, especially if it is not dark in colour, should be tested for porphyrinogen as well as hæmatoporphyrin.

Gunther distinguishes different causes for hæmatoporphyrinuria. In the cases appearing early in life there seems to be some congenital functional or organic defect of the liver which allows the hæmatoporphyrin to circulate, and in the cases appearing later in life the defect in the liver may be acquired. **Königstein** and **Hess** report a case of hydroa vacciniforme in a boy due to congenital syphilis of the liver leading to hæmatoporphyrinuria, and **Gunther** records an acquired case due to alcohol affecting the liver. There are also the cases due to sulphonal and lead poisoning. The eruption in hydroa vacciniforme is provoked by the ultra-violet rays of the spectrum. **Martenstein** found that all the ultra-violet part of the spectrum produced the eruption, but not the alpha, beta, or gamma rays of X-rays.

As showing the effect of ultra-violet rays on the serum, **Baroni** and **Jonesco** showed that these rays could increase the antisensitising properties of horse serum. **Doerr** and **Moldovan** found that the rays could also disturb the faculty of the serum to produce precipitins and passive anaphylaxis. They also demonstrated that if antigens and antibodies were exposed to ultra-violet rays, a diminution occurred in their reactive properties. **White** and **Kanoki** both found an eosinophilia in the blood in cases of hydroa vacciniforme. That fact supports the sensitisation theory.

During the last 2 years 4 cases of hydroa æstivale have been seen in Sir Norman Walker's department at the Royal Infirmary, and in only 1 was hæmatoporphyrin present in the urine. In 1 the urine was mixed with sheeps' red-blood corpuscles and exposed to sunlight, but no lysis occurred. In 1 private case of hydroa vacciniforme in a girl, aged 6 years, no hæmatoporphyrin was found in the urine. Some blood was withdrawn from a vein and Dr. Hedley Wright kindly tested it for me at the Royal College of Physicians' Laboratory. The serum and red-blood cells were separated and the latter washed. The serum was divided into quantities of 0·2 cc. undiluted and

in dilutions of 1 in 5, 1 in 10, and 1 in 20, and mixed with 0·4 cc. of a suspension of the washed red-blood cells. As a control, similar dilutions of syphilitic serum and normal saline were used. One set of tubes was exposed to sunlight and the other kept in the dark. No hæmolysis occurred in any in 12 or 24 hours, but a slight " pinking " of the patient's serum dilutions occurred in 3 days, probably bacterial. This result was negative, but the tubes used were ordinary glass ones and possibly did not allow sufficient ultra-violet rays through to affect the serum. As suggested by the cases of buckwheat poisoning in animals, I went into the question of diet in this child. As there was no buckwheat in the diet, it was thought advisable to exclude ordinary wheaten flour and oatmeal. The child was given rice bread and scones, and biscuits made from rice flour. The parents state that when on that diet the skin was certainly distinctly less sensitive to light than previously. This is only an isolated case, but I think it is worth investigating in similar cases whether alteration in the diet may not cause improvement in such cases. A substance similar to the phyloporphyrin found in buckwheat may occur in ordinary wheat or oatmeal and be responsible for some cases of light dermatitis or hydroa.

Summary

1. Hydroa vacciniforme or æstivale is associated with hæmatoporphyrin or porphyrinogen in the circulation and urine.

2. From analogy with buckwheat poisoning this porphyrinogen acts as a sensitiser and leads to the eruption.

3. The presence of a blood eosinophilia, hæmolysis of red-blood cells by photodynamic substances, the effect of ultra-violet rays on antigens and antibodies all favour the sensitisation theory.

4. The hæmatoporphyrinuria is probably due to some congenital or acquired defect of the liver.

5. The effect of certain substances in the diet requires further investigation in eruptions due to sunlight.

PELLAGRA

In pellagra the skin eruption is produced by exposure to the sun. The disease is by no means rare in Scotland. Several

PELLAGRA

cases are at present in Scottish asylums, and every now and then cases are seen at the Edinburgh Royal Infirmary. A few months ago a very typical case was admitted to Sir Norman Walker's ward in the last stages of the disease. The Plate facing shows the arms of a typical case which was admitted to the Royal Infirmary some years ago.

I do not propose to go into the much discussed subject of the causation of pellagra. Recent work supports the theory of a dietary insufficiency. There is evidence, however, that in pellagra some toxin is circulating which, when exposed to light, causes the skin eruption. Experiments have been performed in Italy to try to demonstrate anaphylactic phenomena by injecting pellagra patients and animals with extracts of maize. **Volpino,** in 1912, showed that injection of a watery extract of spoiled maize caused a definite reaction of hypersensibility with rapid pulse, rise of temperature, dyspnœa, diarrhœa, and aggravation of pre-existing eruption. This reaction was not produced by injection of extracts of sound maize nor by injection of spoiled maize in normal individuals. **Volpino, Mariana, Bordini,** and **Alfrago** failed to produce passive sensitisation of guinea-pigs by injecting them with serum of pellagra patients. **Cesabianchi** and **Vallardi** also found that guinea-pigs chiefly or entirely fed on maize, sound or spoilt, show after a certain time a very marked sensitiveness to injections of maize extracts. They found it to be a specific reaction only occurring in animals fed on maize. **Rondoni** also found a heightened sensitiveness in pellagra patients to injection of maize extracts.

Therefore there is some evidence that in pellagra a sensitisation may occur to some toxin in the food. From analogy with the effects of buckwheat in animals, it is probable that in pellagra some photodynamic substance is circulating which acts as a sensitiser of the skin, but at present there is no evidence as to what that substance is.

At the meeting of the Dermatological section of the British Medical Association at Newcastle in 1921 **Dr. Kenneth Wells** mentioned cases of old people who were toothless and could not masticate and who lived chiefly on tea and bread and butter. These persons developed a scaly eruption on the hands when exposed to the sun.

I have also seen an eruption very like pellagra (pseudo-pellagra) in alcoholics. These cases suggest that excessive carbohydrate diet or excess of alcohol cause photodynamic substances to circulate and produce a skin reaction with a resulting eruption. In true pellagra similar substances are probably responsible for the eruption, but at present the exact cause of its production is largely speculative.

CHAPTER XV

TESTS FOR CUTANEOUS HYPER-SENSITIVENESS

CUTANEOUS REACTIONS

It is generally accepted now that the presence of a specific cutaneous reaction to any given substance is a sign of hypersensitiveness to that substance. The different diseases in which these tests have been applied will be dealt with first, and then the mechanism and significance of the reaction will be discussed.

The cutaneous reactions in tubercle, syphilis, ringworm, favus, and other fungus infections, dermatitis venenata, psoriasis, and gonorrhœa have already been dealt with under these diseases, but there still remains a considerable number of others.

CUTANEOUS REACTIONS IN TYPHOID INFECTIONS
TYPHOIDIN TEST

A great deal of work has been done on this subject, and the results are rather conflicting as to the specificity of the reaction and its value in diagnosis. The results are not all comparable, as different strains of bacilli, methods of preparation, and time of reading the reaction have been used by different workers. **Zupnik,** in 1908, was the first to apply the Pirquet test using typhoid antigen. Four cases of typhoid fever all gave positive reactions, and 2 cases who had had the disease many years before gave slight positive reactions. Since then many others have used this method. A preparation called Typhoidin, analogous to old tuberculin, has been chiefly employed. **Gay** and **Force** consider the reaction specific and indicating an existing immunity against typhoid and allied fevers. **Pulay** supports **Gay** and **Force.** He obtained no reactions in healthy individuals, but definite ones in typhoid cases and those convalescent from the disease. In persons

inoculated against typhoid he obtained reactions, but they were often slight. Patients who had had typhoid reacted more strongly than those only inoculated against it. **Kilgore** also thinks the reaction specific and an indication of immunity. He considers the degree of reaction to be an indication of the degree of immunity present. **Link** also supports these views. There are many others, however, including **Chauffard** and **Troisier, Goodman** and **Sutter, Entz, Szontagh, Rolly** and **Kraus,** who do not consider the reaction specific. **Chauffard** and **Troisier** obtained reactions in both typhoid cases and normal persons, but the reaction was greater in the typhoid cases. **Kraus** and **Stenitzer,** by animal experiments, showed that a toxin exists in the typhoid bacillus and also in filtrates of cultures. **Entz** found that a high percentage of normal individuals react to various bacterial toxins including the typhoid toxin. **Szontagh** tested 72 children suffering from different diseases, doing Pirquet tests with typhoid toxin, and only obtained marked positive reactions in 4 cases, 1 of which was a case of typhoid, another of epityphlitis, and 2 were cases of scarlet fever. The question has been much discussed as to whether the typhoidin skin reaction is a sign of immunity or not. **Gay** strongly maintained that the reaction was evidence of immunity. **Gay** and **Claypole** consider the reaction to have a distinct relation to protection against typhoid fever. They did comparative intradermal tests on normal rabbits and human beings with sensitised and unsensitised typhoid vaccines. They obtained in most cases greater reactions with the sensitised vaccines. This they attribute to an interaction between antigen and antibody similar to what occurs in the Schick test for diphtheria. Further experiments with rabbits indicate that, in the condition of artificial immunisation against typhoid, the antibodies which combine with the antigen to produce the local reaction are in the circulation, as is shown by the passive transfer to a normal rabbit, by means of serum from an immune rabbit, of susceptibility to this reaction. Also, withdrawal of blood from an immunised rabbit and replacement with the blood of a normal rabbit leads to a loss of the reaction. They do not, however, regard these experiments as indicating the circulatory nature of the antibody in persons recovered from typhoid, who almost invariably react to typhoidin.

Meyer, and **Meyer** and **Christiansen,** found that in the rabbit, which is an animal which does not naturally suffer from typhoid, a positive typhoidin skin reaction does not indicate that the animal will resist a subsequent intravenous injection of typhoid bacilli. They found no definite relationship to exist between the presence of agglutinins and complement-fixing antibodies and cutaneous hypersensitiveness. Allergy to bacterial proteins may be demonstrated in rabbits even in the absence of demonstrable immune body. They think the cutaneous reaction to typhoidin in rabbits is due to sensitisation to the bacterial proteins, and that it is not an antigen-antibody reaction.

Kolmer and **Berge** also found that agglutinins and complement-fixing antibodies are present in the majority of persons reacting positively to the skin test, but that there is no definite relationship between them. Cutaneous reactions were found to persist for a longer time among those who had had typhoid than among those actively immunised by a vaccine. They conclude that while the typhoidin reaction indicates sensitisation to typhoid protein, there is not yet sufficient evidence to warrant its acceptance as an index of immunity. **Nichols** agrees with this, because he found positive typhoidin reactions in soldiers vaccinated with paratyphoid vaccine, and it is well known that paratyphoid vaccine will not immunise against typhoid. Therefore he accepts the protein sensitisation theory of the reaction.

Austrian and **Bloomfield** also failed to confirm **Gay's** work that a positive skin reaction means immunity. The typhoidin test has also been used for the detection of typhoid carriers. **Meyer** found cutaneous hypersensitiveness to typhoidin to be most marked in rabbits infected with the typhoid bacillus. Carriers of bacilli in the gall bladder and liver develop skin reactions which apparently vary directly with the degree of the inflammatory process in the organ. **M'Kendrick,** in a recent article, gives the results of a series of intracutaneous tests with suspensions of bacillus typhosus and bacillus paratyphosus A and B. These results show that positive reactions are very constantly obtained in persons suffering from typhoid fever and in chronic carriers. The test was found to be highly specific, the cases only reacting to the type of organism causing the infection. Only 2 out of 260 control cases gave positive reactions to bacillus

typhosus and none to bacillus paratyphosus. No relationship was found between the skin reaction and the presence of pyrexia in acute cases, or between the skin reaction and Widal reaction in carriers. **M'Kendrick's** results indicate that the skin reaction becomes negative early in convalescence from enteric fever. He suggests that patients convalescing from typhoid fever should be examined for the skin reaction. A positive reaction probably indicates persistence of the infection which may result in relapse or the carrier state. **M'Kendrick** considers a positive skin reaction in apparently healthy persons as suggestive of their being typhoid carriers.

PNEUMONIA

Clough, in 1915, studied allergy in pneumonia. He employed the dried and ground residue of extracts of washed pneumococci before and after precipitation with absolute alcohol. Cutaneous and intracutaneous tests with these extracts on persons suffering from pneumonia yielded variable and inconstant results. **Clough** thought the results were due to the irritant qualities of the extracts, and was of opinion that it was impossible to demonstrate a state of hypersensitiveness to pneumococcus protein by these tests.

Steinfield and **Kolmer** did intradermal tests with pure cultures of pneumococci shaken and emulsified with salt solution : 0·1 cc. of emulsion was injected and positive reactions consisted in the formation of a definite papule with an area of erythema of more than 1 cm. in diameter. The reaction persisted for 4–5 days. Positive reactions were observed in 30 per cent. of 19 cases of lobar pneumonia. True reactions were not observed among normal persons or those suffering from various chronic diseases. The presence of pneumococci in the upper air passages during health does not sensitise the individual so far as could be detected by skin tests.

Weiss and **Kolmer** used the endocellular hæmolytic toxin of the pneumococcus freshly prepared for each test. Intracutaneous injections in doses of 0·1 cc. led to a local erythema and hæmorrhagic œdema. These reactions were seen on the 5th to the 13th day of the disease, *i.e.* 2 days before and 6 days after the crisis ; but patients recovering by lysis reacted as late as the 32nd day.

In children the reaction became negative immediately or 2 days after the crisis. In no case did any control react positively. In general, the reaction was positive in all active cases of pneumonia.

Weil also did a series of intracutaneous tests, using a much weaker extract than did **Clough.** The injection was immediately followed by a cutaneous blush which was present both in pneumonia cases and controls. This he considered an irritation reaction similar to that seen by **Clough**. The true reaction occurred after 24 hours as a papule with an area of erythema round it. **Weil** obtained no true positive reactions during the course of the disease, but in a considerable percentage of cases reactions were found after the crisis. The reaction could be induced exceptionally within 24 hours after the crisis, but usually only appeared after an interval of 2 or 3 weeks. Normal individuals sometimes gave a positive reaction presumably from a previous mild or unidentified attack. Contrary to the experience of **Steinfield** and **Kolmer, Weil** suggests also that these reactions in normal individuals might be due to the presence of the pneumococcus in the upper air passages. **Weil** thinks that 2 types of skin reaction occur from pneumonia vaccines. The one (as shown in **Clough's** work) is due to the toxin and similar to the Schick reaction in diphtheria. A positive reaction of this type indicates a deficiency in the mechanism of defence. The other is a true reaction, which is a sensitisation phenomenon, the same as in the tuberculin skin reactions. He thinks that the absence of a true reaction during the disease is not due to absence of antibody but to the coexistence of sufficient antigen in the cells to prevent the reaction. After the crisis, when the antigen has disappeared, antibody becomes available for the production of the reaction. He considers the absence of the reaction during the febrile stage of the disease as analogous to the absence of the Pirquet reaction in acute miliary tubercle, and, as the reaction does not occur till after the crisis, it has no value in diagnosis.

PERTUSSIS (Whooping Cough)

Modigliani and **De Villa,** in 1921, did a series of intracutaneous tests using a solution of bacillus pertussis in sterile distilled water.

Autolysed bacilli coli were used as control. In 38 children suffering from whooping cough all reacted positively. The intensity of the reaction was greatest in the early stages of the disease. In 58 immune children there were no positive reactions.

Orgel did similar intracutaneous tests with a vaccine of bacillus pertussis containing 2 billion organisms to each cc. He obtained reactions which he considers specific in cases of whooping cough. **Riesenfeld,** in 1923, used a pertussis vaccine of the Bordet-Gengou bacillus. In 60 cases of whooping cough 53 reacted positively. Thirty-nine cases of whooping cough were also tested intracutaneously with staphylococcal vaccine and 35 of them reacted positively. He found that the reaction to bacillus pertussis vaccine was not specific, as it was positive in some children who developed the disease later. The test was found also not to be a reliable guide as to a natural or acquired immunity to the disease.

LEPROSY

Stein, in 1916, published a very good record of the work done on sensitisation in leprosy. **Babes** and **Scoltz** and **Klingmuller** made an extract from leprous nodules called Leprin similar to tuberculin. Injection of this extract caused no reactions in cases of leprosy. Then **Babes** and others used tuberculin, as the tubercle bacillus is allied to the leprosy bacillus. Injection of tuberculin subcutaneously led in some cases to a general reaction with temperature, but it was found that it required a larger dose of tuberculin to produce a temperature reaction than in tubercle. In no case has a focal reaction in leprosy been seen after injection of tuberculin, although local and general reactions may occur. Many workers such as **Stein** and **Arning** consider the local and general reaction to tuberculin in leprosy cases to be due to a concomitant tuberculosis. **Rost, De Beurmann,** and **Gougerot** used cultures of a glycerine extract of leprosy bacilli (Leprolin) which on injection caused general and focal reactions in both forms of leprosy. **Dyke, Much,** and others made similar injections of Nastin (extract of streptothrix leproides) and obtained general reactions. But as these general reactions might be due to toxins contained in the extracts, it is doubtful if these reactions indicate sensitisation. **Photinos** and **Michaelides** did tuberculin

Pirquet tests in 204 leprosy cases and obtained positive reactions in 118. **Nicolle** and **Teague** obtained negative cutireactions, using a leproma extract. Therefore, **Stein** " concludes that, as regards allergic reactions in leprosy, cutaneous and subcutaneous inoculation with leproma extracts produces no reaction. Inoculation with tuberculin, leprolin, and nastin often leads to marked reactions on later injection, but their specificity is doubtful."

Stein also reports numerous cases of the so-called leprosy erysipelas. These cases show a sudden high temperature, with headache. In a few hours a bright red area appears on the skin. It is sharply defined and spreads rapidly. The redness diminishes and is replaced by a paler flat infiltration like erysipelas, but with a less defined margin. If it persists, blisters (which contain no leprosy bacilli) appear on the surface. Some of them change into lesions like furuncles, with ulceration and loss of substance. The pus from these lesions contained countless acidfast bacilli. The infiltration gradually disappears from the lesions and scars may be left, but **Stein** never saw leprosy nodules develop on these areas. One erysipeloid attack was followed by another. **Stein** did intradermal tests using an extract from leprous lymph glands, and 2 cases gave marked positive reactions. These reactions were not present after the attack. He therefore concludes that the so-called leprosy erysipelas is due to an allergic condition of the skin, and corresponds to the erythematous and papulo-necrotic tuberculides of tubercle.

The fact that in the ordinary case of nodular leprosy the lesions are teeming with bacilli is very much against the patient being sensitised. If he were sensitised, the presence of the bacilli in the skin would cause a more marked reaction, which would inhibit the growth of the organism. In tubercle of the skin very few organisms are present in the lesions, because the sensitisation reaction tends to check their growth and spread. Similarly, in tertiary syphilis the gumma contains very few spirochætes.

Therefore, from the negative results of attempts to produce cutireactions with leprous extracts and the presence of large numbers of bacilli in the lesions, if any sensitisation occurs in leprosy it must be very slight. The various reactions in leprosy from tuberculin are not a reliable guide, as it is admitted that many cases of leprosy are also infected with tubercle.

HYDATID DISEASE

The rashes produced in cases of hydatid disease from rupture of a cyst have already been referred to (p. 42). The fact that these rashes occur show that the skin is sensitised. It is, therefore, to be expected that such cases will give a skin reaction. **Serra** recommends the intradermic test, introduced by **Casoni,** as an accurate method of diagnosing hydatid disease: 0·5 cc. of clear fluid from a hydatid cyst is injected intradermally into the skin of one arm and the same quantity of normal saline solution as a control into the other arm. In positive cases within a few hours an extensive erythema with œdema appears round the area. There is also usually considerable itching. The reaction takes several days to subside. It has never been found positive in any other condition than hydatid disease, but it may be absent if the cyst wall is abnormally thick or calcified so that there is not sufficient absorption from the cyst to sensitise the patient. The test is extremely useful in the diagnosis of doubtful cases. A positive result may be taken as proof of the disease, but a negative result does not absolutely exclude it.

INFECTIOUS DIARRHŒA

Baker, in 1917, did intracutaneous tests with the organism of infectious diarrhœa in 33 cases. The reaction was positive in 85 per cent. of the cases and negative in all the controls.

ULCERS DUE TO PENICILLIUM GLAUCUM

Rebaudi and **Podesta** report a case of multiple ulcers of the legs in a girl 14 years of age. From the ulcers a culture of penicillium glaucum was obtained. A filtrate of the fungus culture gave a positive intradermic reaction.

MENINGOCOCCUS INFECTIONS

Karsner and **Ecker** quote **Gay** and **Minaker's** work on the intracutaneous reaction for the detection of meningococcus carriers. They used an emulsion of powdered meningococci of 5 strains. They obtained reactions in 64·5 per cent. of known carriers and in 26·4 per cent. of non-carriers. They do not

consider the reaction useful in diagnosis, but suggest that in carriers there is some degree of acquired resistance.

CUTANEOUS REACTIONS TO VACCINE VIRUS

In his work on vaccination **Jenner** noticed that in persons who had been previously vaccinated, a second vaccination produced a mild local reaction only. **Pirquet** investigated the matter thoroughly and showed that on revaccination the patient did not develop the usual vaccine vesicles, but showed a reaction with papule formation and erythema which subsided in a few days. This is an example of allergy. An attack of smallpox or vaccinia by vaccination alters the reactivity of the skin so that it becomes sensitised, and any further attempt at revaccination produces a reaction analogous to the tuberculin Pirquet reaction. These are the cases of vaccination which do not "take." The reaction is often called an immunity reaction, but it is really a sign of hypersensitiveness. The reaction is protective as it prevents a reinfection with vaccinia.

MALIGNANT DISEASE

Ravenne, in 1912, took a non-ulcerative carcinoma of the breast, cut it up and pounded it in a mortar and added physiological salt solution 1 in 4. This was shaken for 24 hours, filtered in a wide-pored filter, and the filtrate used for skin tests. Twenty-four patients with carcinoma of lip, larynx, œsophagus, nose, rectum, breast, stomach, or pancreas were tested by the Pirquet method. Only 2 gave positive reactions. The other 22 cases, although the test was repeated, were negative. In 20 control cases suffering from diseases other than carcinoma the tests were all negative. In 21 cases of carcinoma tested by the intradermal method 6 reacted positively, and 12 control cases were all negative.

Further evidence is necessary before any conclusions can be drawn as to the value of the test.

ULCUS MOLLE (Soft Sore)

Ito, in 1913, did a number of experiments with Ducrey's bacillus. Rabbits were injected every 5 days for 3 times with an

emulsion of killed strepto-bacilli. A fortnight later intracutaneous injection of the strepto-bacillus emulsion gave positive reactions which did not occur in control animals. In man similar injections of strepto-bacillus vaccine in an individual who had never had soft sore caused the appearance of a marked reaction on testing the skin intradermally 10 days later. In 11 cases of ulcus molle with buboes all gave a strong positive reaction to the intradermic test. **Ito** considers the reaction specific and an aid in confirming the diagnosis of soft sore.

Ito found that by previous treatment with strepto-bacillus vaccine no active immunity can be produced, but, as already shown, by previous treatment with strepto-bacillus vaccine or by a previous soft sore infection hypersensitiveness may result. Passive anaphylaxis can be produced both by the serum of guinea-pigs sensitised to the strepto-bacillus and by the serum of patients with buboes. The precipitation, agglutination, and complement-deviation tests both with patient's serum and the serum of previously vaccinated animals did not yield any noteworthy results.

CUTANEOUS TESTS IN PREGNANCY

Englehorn and **Wintz,** in 1914, did cutaneous tests with extracts of placenta in cases of pregnancy. They claimed to obtain favourable results as to the specificity of the reaction. **Esch** and **De Jong** made similar tests, but could not confirm these observations. Likewise **Falls** and **Bartlett** made cutaneous and intracutaneous tests with whole placenta and various fractions of placenta. Like **Esch** and **De Jong** they failed to find any evidence of specific sensitisation. They conclude that the pregnant woman is certainly not a sensitised woman in the usual sense. **Stokes** explains the non-specificity of these reactions on the antiferment-adsorption theory of sensitisation. He quotes **Eggstein** and **Petersen's** experimental work on the antiferment-adsorption capacity of the placenta. In pregnancy there is known to be a rise in antitryptic-titer in the serum which also supports the theory of antiferment-adsorption and might explain the want of specificity in the reaction.

CUTANEOUS REACTION IN CANINE DISTEMPER

Kolmer, Harkins, and **Reichal,** in 1916, did intracutaneous tests in dogs with distemper, using the bacillus bronchisepticus (Ferry-M'Gowan), which is the probable cause of distemper. The highest percentage of positive reactions occurred among dogs suffering from distemper when the tests were made and amongst those known to have had distemper. These observers think that the test may prove of value in the diagnosis of distemper and as an index of previous infection in an animal. The test has probably no value as an index of immunity, as an animal showing a positive reaction is still susceptible to a relapse of the disease.

SCHICK TEST FOR DIPHTHERIA

The Schick test is not really comparable with the cutaneous tests being discussed as it is not a sensitisation reaction, but depends on the presence or absence of the diphtheria antitoxin. The so-called pseudo-reaction in this test was first described by **Park, Zingher,** and **Serota.** It consists in a small area of redness and infiltration at the site of injection within 24 hours. Injection of bouillon alone gives this reaction. They consider it an allergic reaction due to the proteins in the broth used to prepare the diphtheria toxin. **Kolmer** and **Moshage** and **Weaver** and **Maher** agree with this view. These pseudo-reactions can be detected by doing control tests with the broth only.

CUTANEOUS PROTEIN TESTS IN ECZEMA, URTICARIA, ETC.

Before discussing these tests I propose to put on record my own experiences with them. I used the Arlington Chemical Company's products in powder form. A small rounded burr was used to scarify the skin short of drawing blood; a drop of deci-normal sodium hydrate solution was placed on this with a glass rod, then a few grains of the protein powder on a thin glass rod were mixed with the sodium hydrate and gently rubbed in. The powder dissolves immediately in the alkaline solution. The tests were done as a rule on the front of the forearms, the control, into which

the sodium hydrate solution only was rubbed, being placed near the elbow and the others lower down in 2 or 3 rows at intervals of about an inch. The control was placed near the elbow, as I can confirm the observation of other workers that that area of skin is slightly more sensitive to irritation than the rest of the arm. Fifty different proteins in all were used. Most of the cases were tested to about 30 of these, a selection being made of the substances most likely to react according to information obtained from the patient. Patients were not tested to foods which they said they never ate. Although the tests are quite easy to carry out, the chief difficulty which I had, was to know what constitutes a positive reaction. No reaction was considered positive unless it was at least twice the size of the control. Reactions only very slightly larger than the control were marked as doubtful and looked upon as probably negative. Some of these doubtful reactions were repeated and in every case turned out to be negative. When a positive reaction was present there was no doubt about it (Plate opposite). An irregular wheal was produced with a wide area of erythema spreading out irregularly in all directions for a considerable distance. A reaction was not considered positive unless both wheal and erythema were present. A wheal alone or erythema alone was not considered positive. The reaction was usually quite distinct in 10 minutes, at its maximum in 15–20 minutes, and was fading in a little over half an hour. I have never seen delayed reactions as described by **Freeman** and others, although the cases were carefully examined for them. Each worker has his own standard of what constitutes a positive reaction. **C. J. White** considered a papule sufficient, but as he often found this on the control it is obviously a false standard. **Strickler** and **Goldberg** insist on the reaction lasting 48 hours before they consider it positive, but these were intradermic and not the ordinary cutaneous tests. **Schloss, Talbot, Smith,** and others considered the reaction positive even although lasting about half an hour or so. **Foote** thinks the reaction is not positive unless it is 3 times the size of the control. But most of those who have used the tests extensively, and especially in asthma, are agreed that the reaction is a wheal at least half as large as the control surrounded by a zone of erythema.

CUTANEOUS TESTS.

	Dermatitis.																		Psoriasis.				Eczema.						Derm. Herpetif.
Sex and Age	M. $1\frac{5}{12}$.	M. $\frac{4}{12}$.	F. 3.	F. $1\frac{8}{12}$.	M. $\frac{9}{12}$.	M. 5.	F. 7.	F. 10.	M. 11.	M. 14.	M. 9.	M. 7.	F. 22.	F. 22.	F. 22.	M. 27.	M. 32.	M. 40.	M. 55.	F. 60.	M. 22.	M. 8.	F. 18.	M. 32.	M. 42.	F. 2.	M.	M.	F. 26.	M. 30.	F. 35.	F. 65.	F. 89.	M. 56.
Name	K. G.	J. A.	M. A.	W.	M. N. S.	H. H.	N. S.	D. P.	G. W.	J. M.	J. F.	H. B-J.	M. D.	A. S.	M. L.	A. B.	R. G.	B. B.	A. M-F.	Mrs D.	E. A.	D. B.	H. W.	R. B.	W. J. M.	R. M-C.	A. S.	J. T.	C. L.	A. S.	Mrs K.	Mrs R. D.	Mrs B.	W. T.
Control	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–												–			
Egg-white		–	–	+		–	+					–	–	–				–					+	–					–			
Egg-yolk	–			–	–					–				–	–	+	–	–	–	–		–	+	–					–			
Milk (cow's)		–	–	–	–				–		–			–															–			
Lactalbumin		..	..	..		..	..	..	..	..	..	..	..		..	..	..	..	..	..	..	..		..		..	..			..			
Cheese	..	..	..	..	..			–		–	–														–				–			
Chicken	..	..	..	..	..	+		–			–		–									–	+	–	–				–			
Veal	..	..	..	..	..		–		–		–			–					..	–			±	–	–				–			
Beef					–						–	–			–	+	–	–	–	–					–				–			
Pork	..	–		..	..						–														–				–			
Lamb	..	–		..	..	±		..	–		–		–	–											–				–			
Herring	..	..	..	..	..			..			–	–	–	–					..						–				–			
Haddock	–	..	..		..	–	–	–			–								..			–	–		–				–			
Cod	..	..	..	..	..	..	..	..	..		..		–	..					..			–	+		–				–			
Salmon	..	..	..	..	..	..		–	–		–	–		–		–	–		..						–				–			
Sole	..	..	..	..	..	..	..	–	–		±		–						..						–				–			
Mackerel	..	..	..	..	..	..	..	..		..	..	..	..	–					..						–				–			
Lobster	..	..	..	..	..	..	..	..	..	..	..	..	..						..						–				–			
Crab	..	..	..	..	..	..	..	–	–	..	–	..	..	–					..						–				–			
Oyster	..	..	..	..	..	..	..	..	..	..	..	..	..		..	..	..	..	..	..					–				–			
Wheat	–	..	–	+	–	±	–	–	–	–	–	–	–	–	–	+	–	..	–	–					–				–			
Rice	–	..	..	–	..		..	–	–	–	–	–	–	–				–	–	–		..	..						–			
Barley	..	..	..	–	..	..	–	–	–	–	–	–	–	–				–	..			..	±	–	–				–			
Oat	±	–	–	–	..		–	–		–	–	–	–	–	–	–	–	–	–	±		..	–		–				–			
Pea	..	..	..	..	..	..	..	–	–		+	–	–	–	–	–	–	..	..	–		..			–				–			
Bean	..	..	..	..	..	..	–	–	–	–	–	–	–	–	–	–	?	..	..			..	–		–				–			
Lentil	..	..	..	..	..		..	..			±	–	–	–	..			..	..	..	–	–	–		–		..	..	–				
Potato	–	..		–	..	–	–		–	–	–	–	–	–	–	–	–	–	–	–		..	–		–				–				
Beetroot	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..	..		–	–	..		..				–				
Cabbage	..	..	..	–	..	..	–	–	–	–	–	–	–	–	–	–		..	–			..	–		–				–				
Carrot	..	..	..	–	..	..	–	–	–	–	–	–	–	–	–	–		..	–			–	±	–					–				
Celery	..	..	..	..	..	..	..	–			–		–	..	..	–		..	..											..			
Cucumber	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..	..	..	..	..		–									..			
Strawberry	..	..	..	..	..	–	..	–			–	–	–	–	–			..	..										–				
Tomato	..	..	..	..	..	..	..		–	–	..	–	–	–	–	+	–	..	..	..	–		..							–			
Banana	..	..	..	..	–	..	..				..	–	–	–	–	–	–	..	..		..		..							–			
Orange	..	..	..	..	–	..	..	..	..	–	..	–	–	..	..	..	–	..	..	..	–		..							–			
Almond	..	..	..	..	..	..	..	–	–	..	..	–	..	–	–			..	..		–	..	..							..			
Brazil nut	..	..	..	..	..	..	..	..	..	..	..	..	..	–	–	–	..	..			–	..	..							..			
Cocoa	..	..	..	..	..	..	–	–		..	–	–	–	–	–	..	–				–		–		–	–				..			
Cattle hair	..	..	..	..	..	..	..	..	..	..	..		..	..	..	..	..	..	..		–	..	..		–					..			
Chicken feather	..	..	..	–	–	..	..	–	..	–	..	–	..	..	..	..	–		–		–	..	..		–					..			
Dog hair	..	..	..	..	..	..	..	..	–	..	–	–	..	..	..	..	–	–	..	..	–	..	..		–					..			
Goose feather	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..	–		–	..	..		..					..			
Horse dander	..	..	..	–	..	..	..	..	..	..	±	–	..	..	..	..	–	–	..	..	–	..	..		..					..			
Rabbit hair	..	..	..	..	..	..	..	..	..	..	..	–	..	..	..	..	..	..	..	–	–	..	..		–					..			
Sheep's wool	..	..	..	–	..	..	..	..	..	..	..	–	..	..	–	..	–	–	..	–	+	..	..		–					..			
Turnip	..	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..	..	..	..	..	..	..	..		–					..			
Onion	..	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..	..	..	..	..	..	–	..		..					..			
Tea	..	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..	..	..	..	..	..	–	–		..					..			
Sugar	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	–	..		..					±			

+ = Positive. – = Negative. .. = No test made with that protein.

To face p 253.

My results are shown on the accompanying table. Thirty-four cases were tested, consisting of 21 cases of chronic dermatitis (eczema), 4 of prurigo, 8 of urticaria, including urticaria papulosa, and 1 of dermatitis herpetiformis.

DERMATITIS CASES

1. Five of these cases were children under 3 years of age, with the ordinary infantile eczema. Two gave an entirely negative result, 2 gave doubtful reactions, and 1 was positive to egg white and wheat. Cutting these articles out of the diet of the last case, however, had no effect on the dermatitis.

2. Of the 7 cases between the ages of 5 and 14 years, 3 were entirely negative, 2 gave doubtful (probably negative) reactions, and 2 gave definite positive reactions. Of the negative cases, 1, J. M., age 14, a very chronic and extensive dermatitis, later recovered completely after a course of intestinal lavage at Harrogate, so that he was probably not a food case, but a sensitisation to a bowel infection. Another of the negative cases, H. B.-J., age 7 years, also suffered from asthma. He had his tonsils and adenoids removed, but with no improvement on the eruption. A sister of this patient, however, who also had suffered from dermatitis and asthma, had recovered completely after her tonsils and adenoids were removed. Of the positive cases, H. H., age 5 years, gave a very marked reaction to chicken, but removal of chicken from the diet, and also feeding him on it, had no effect on the eruption. The case N. S., aged 7 years, is the one shown on Plate facing p. 252. In this case there was a marked reaction to egg white and egg yolk; also to beef and chicken; but these reactions are not shown in the cast as they were done on the other arm. This case was a most successful one. Removal of egg, beef, and chicken from the diet caused the eruption to disappear very rapidly, although the child had suffered since infancy.

3. Of 9 adults between the ages of 22 and 60 years only 2 gave positive reactions. One reacted to egg yolk, beef, wheat, and tomato, the other to egg yolk and sheep's wool. Both these cases also suffered from asthma. In the first case, dieting on the lines suggested by the eruption had no effect upon it. Similarly,

cutting eggs out of the diet had no effect on the second case, and rubbing wool on the skin did not produce a dermatitis, nor did inhalation in close proximity to wool produce an attack of asthma.

These results are rather disappointing when compared with those recorded by others. **Ramirez,** in 78 cases of eczema in children under 2 years of age, had 30 positive results.

O'Keefe, in 70 cases of eczema, found 41 per cent. positive, and in breast-fed infants, out of 41 cases, found 61 per cent. were positive to one or more proteins. **Blackfan**, in 27 cases in infants and adults, found 22 reacted positively. **C. J. White** found 30 per cent. were positive, but, as already mentioned, I do not consider his results reliable. **Schloss,** in 77 cases of eczema in children, found that 50 were positive. **Talbot,** in 16 cases of eczema in infants and children, found that 87 per cent. gave positive reactions to egg white. **Fox** and **Fisher** tested 80 cases by the cutaneous method in adults and obtained 19 positive reactions. **Engman** and **Wander** obtained positive reactions in 78 per cent. of cases of infantile eczema, and in 38 per cent. of chronic extensive eczemas in adults. **Strickler** did intradermic food tests in 46 cases of eczema, and obtained positive results in 80 per cent.

The published results of others therefore show on the whole a larger proportion of positive results than I obtained, but all agree that the younger the patient the more likely is he to react to a food protein, and multiple reactions are the rule rather than the exception.

PRURIGO (OF HEBRA)

Four typical cases of prurigo were tested and only 1 gave any reaction, and that to egg white, egg yolk, and cod. Exclusion or inclusion of these foods in the diet did not affect the eruption in any way. I can find no other record of food tests in cases of prurigo.

URTICARIA

Out of 8 cases not a single positive reaction was obtained. Five gave doubtful, probably negative, reactions. One of these cases has already been mentioned under urticaria and eventually recovered completely after 2 teeth were extracted.

Engman and **Wander** obtained positive reactions in 79 per cent. of their 19 cases of urticaria. **Schloss** in 60 cases of urticaria only obtained positive reactions in 10, and in 14 cases of angio-neurotic œdema only 2 gave positive reactions. These 2 cases both suffered from the eruption when fed on the protein to which they reacted. **Strickler,** using the intradermic method, obtained 8 positive reactions in 10 cases.

The results of others are more encouraging than in my cases. One of the chief difficulties in urticaria is that many cases react so markedly to the mechanical irritation produced in doing the test that it is impossible to gain any information from the tests.

DERMATITIS HERPETIFORMIS AND OTHER SKIN DISEASES

I have only tested 1 case, and this case gave doubtful reactions to veal and barley. **Engman** and **Wander** state that in dermatitis herpetiformis the number of cases reacting positively is negligible. Eleven cases were examined, and only 1 gave a slight reaction, and that to horse dander.

In several other skin diseases the protein skin tests have been applied in a few cases. **Engman** and **Wander** found that in erythema multiforme and pemphigus the number of cases reacting was very small. **Schloss** tested 7 cases of erythema multiforme, and in 1 case which reacted to pork the elimination of that article from the diet cured the case. This patient was later immunised by injections of pig's blood serum.

Coke also reported 2 cases of pruritus ani, 1 of which reacted to potato and the other to pork. On removing these articles from the diet or feeding the patient on them the condition disappeared and reappeared accordingly.

ASTHMA AND HAY-FEVER

Cutaneous protein tests have been used extensively in asthma and hay-fever by **Walker, Ramirez,** and others. The tests have been found on the whole to be more reliable than in skin diseases. The results with food proteins, pollens, and animal hairs give very useful information as to the cause of these conditions. In chronic cases of asthma, however, the condition

is complicated by secondary infection of the respiratory tract with organisms, so that removal of the food from the diet does not always cure the asthma.

OTHER METHODS OF PERFORMING SKIN TESTS

Instead of using a burr to make the scarification for the cutaneous tests, some make a series of small scratches with a needle, whilst others make short superficial cuts with a sharp knife. The latter method has the advantage of eliminating the effect of trauma from the reaction.

The intradermic method by which the dissolved protein is injected with a sharp needle into the skin has been used especially in asthma.

Most of the work in protein tests in skin diseases has been done by the cutaneous method. **Chandler Walker** and **Adkinson** report that the intradermic test is much less specific than the cutaneous one. It is too sensitive, is more difficult to do, and may cause the patient considerable discomfort. It is also not practicable where many proteins have to be tested. It gives reactions which do not separate closely related proteins, and therefore the ordinary cutaneous tests are to be preferred.

I used powdered extracts of the proteins dissolved in alkali applied to the skin, but numerous firms have now put on the market proteins in solution in capillary tubes. Besides being more expensive where many tests have to be applied, the method is much more cumbersome than the use of the powders. To get over this difficulty, tests have been made with groups of proteins containing several allied substances in one solution. If a reaction occurs to one group, then one must test again with each member of the group.

THE VALUE OF CUTANEOUS PROTEIN TESTS IN SKIN DISEASES

In the 34 cases which I tested only 6 reacted definitely positively, viz. 5 cases of dermatitis and 1 of prurigo. That, of course, does not necessarily mean that all the negative cases were not sensitised to something. One cannot test every case

to every possible protein, and there is always the possibility that the patient might be temporarily desensitised. The reaction seems to vary very much from day to day, and there are numerous cases recorded where it was present one week and absent the next.

Multiple reactions raise many interesting points. As in the plant dermatitis, there seem to be group reactions. A guinea-pig sensitised to sheep serum will also react, but less violently, to goat serum. **Wells** and **Osborne** have shown that preparations of legumen from the pea and vetch are very similar, if not identical, and also the gliadin contained in wheat and rye. They have also obtained cross reactions between gliadin from wheat and rye, and hordein from barley. **Holobut** has found the same group reactions in bacterial proteins. He found that reactions could be produced in typhoid cases with bacillus coli and cholera vibrio as well as with bacillus typhosus. **Freeman** has shown that an asthmatic sensitive to horse serum will give a marked skin reaction to that serum and also a distinct but lesser reaction to the sera of all the equidæ.

Wells is of opinion that multiple reactions are the result of common groups in the protein molecule even though the proteins may appear to be chemically distinct. These facts may account for some of the multiple skin reactions where a patient reacts to wheat, oatmeal, and barley, or other cereal.

On the other hand, these multiple reactions may be due simply to a multiple sensitisation, because if a person can be sensitised to one protein he may be sensitised equally easily to several. The fact that a case of dermatitis gives a positive skin reaction to a certain food does not necessarily imply that that food is causing the dermatitis. The reaction persists long after the food has ceased to cause symptoms. In cases of infantile eczema, where multiple skin reactions occur, the disease may not always be due to the same protein all through its course. These cases notoriously have remissions and exacerbations, and these could be explained by the child becoming sensitised, say, to egg, and having a dermatitis from egg for several weeks. If continuously fed on egg, the child would become desensitised and the eruption improve or disappear, the skin test, however, still remaining positive. Meantime he might become sensitised to another food such as wheat, and so the process goes on till at

about 3 years of age, when these cases usually recover, the child has become desensitised to all the common foods.

ARE THE PROTEIN SKIN REACTIONS SPECIFIC?

Blackfan, in 43 persons (infants and adults) who had never had eczema, found that only in 1 did he get a positive skin reaction. This case might, however, have previously had some other condition, such as urticaria, which might have accounted for the reaction. **Baker** also did a series of food tests in a large number of normal children and found that "in the normal child the incidence of protein sensitisation is negligible. Therefore we may assume that a positive reaction to any protein means that the patient is or has been sensitive to it."

VALUE OF THE REACTIONS

To be of any value from the therapeutic point of view positive reactions should enable us so to regulate the diet as to cure the condition. In my 5 positive cases in only 1 did cutting out the foods indicated by the skin tests cure the condition and that in 10 days or so. In the other 4 cases dieting had no effect, not only so, but feeding the patients on foods to which they reacted did not make the skin eruption any worse.

Ramirez found in 30 cases of eczema, as a result of dieting based on the skin reactions, that 10 were cured, 12 improved, and 8 unaffected. **Engman** and **Wander** found the tests of great therapeutic and diagnostic value in urticaria and eczema, but the method requires time and patience. In every instance where the diet could be absolutely controlled, as in infants, the results were excellent, but in adults it is very difficult to control the diet properly, because the patient, sensitive to a food such as eggs, may stop eating eggs, yet continue to take them in small quantities in other foods such as cakes, puddings, etc. **Strickler** found that in 46 cases of eczema showing positive reactions in 70 per cent., 50 per cent. of these were in greater or less degree benefited by change of diet as indicated by the reactions. In urticaria only the acute cases benefited by suitable dieting.

Positive reactions have been obtained by various observers to practically all kinds of foods, both animal and vegetable.

Egg, however, seems to be the commonest food to give reactions. **O'Keefe** obtained a reaction to egg in 41 per cent. of his cases. **Talbot, Schloss,** and others agree with this, but **Ramirez** and **Fox** and **Fisher** found that the proteins of cereals and vegetables were very frequently the cause of positive reactions.

THE HISTOPATHOLOGY OF POSITIVE CUTANEOUS REACTIONS

Strickler, and **Strickler** and **Asnis,** examined the skin microscopically in tuberculin Pirquet tests, food and luetin tests. They found that in food and tuberculin reactions there was a mononucleated cellular reaction in the more superficial part of the corium with a polymorphonuclear cell infiltration in the deeper parts. In luetin reactions there was found a polymorphonuclear cell infiltration with congestion of the blood vessels and necrosis. They are unable to suggest any cause for the absence of mononucleated cells in the luetin reaction.

Some years ago **Klingmuller,** in Breslau, examined the site of injection of old tuberculin given subcutaneously and found it contained typical giant-cell tubercle nodules.

THEORIES OF CUTANEOUS REACTIONS

The cutaneous reactions are all based on what is known as the "**Arthus** phenomenon." **Arthus** showed that if a rabbit receives 5 cc. horse serum subcutaneously every 6 days, after the first 3 injections there is no reaction at the seat of injection, but after the 4th injection a local reaction occurs with redness and swelling. After subsequent injections a progressively more severe reaction, which may even go on to gangrene, occurs each time. The animal is sensitised by the injections, and the more highly sensitised it becomes the greater the local reaction. This serum skin reaction is used now to test patients before injection of antitoxic sera to see if they are sensitive.

Biberstein and **Oschinsky** describe cases of a local reaction on the first injection of rabbit, guinea-pig, and sheep serum into the skin of human beings. This reaction develops after an incubation period of 7–8 days. They regard these reactions as "local examples" of serum disease.

Krause did a series of experiments to determine the time which elapses between infection and the appearance of cutaneous hypersensitiveness. He injected guinea-pigs with two strains of tubercle bacilli, one virulent causing general tuberculosis, the other benign causing only local gland changes from which the animals recovered rapidly. Animals injected with virulent cultures showed increasing cutaneous hypersensitiveness from the 11th day on till the 46th day when the disease was well advanced. In every case the reaction was more intense than in the animals inoculated with the non-virulent cultures. In the animals injected with the non-virulent cultures the reaction increased as the disease developed, but as the disease came to a standstill and began to heal, the skin reaction became milder but never entirely disappeared. The local cutaneous reactions in tubercle, syphilis, etc., have already been described and need not be further mentioned.

These various reactions may be explained according to any of the theories which are held with regard to anaphylactic shock. If one believes in the production of a poison (anaphylatoxin) in anaphylaxis, then one explains the skin reaction as the reaction between the antigen and the antibody to produce this poison in the skin, leading to a dilatation of the vessels, cell infiltration, and œdema. On the other hand, many explain the phenomenon on the physical theory. This theory explains better than any other the non-specific reactions.

Sellei did a number of experiments by doing cutaneous tests with skin emulsions. He obtained a more marked reaction on injection of a skin emulsion into the person from whom the skin was taken than could be obtained from a skin emulsion from another normal individual. This he believes to be due to selective hypersusceptibility of the normal skin to its own proteins, and suggests the name Homæsthesia for it.

Stokes, like **Sellei,** found that normal skin reacts to intradermal injection of emulsions of normal skin with a reaction similar to the luetin reaction. No constant specific character could be found in normal persons for the response towards their own skin as compared with that to other skin emulsions. The skin emulsion possessed no antigenic properties in a hæmolytic complement-fixation cycle. Attempts to sensitise guinea-pigs

passively to emulsions of skin by means of serum from the donor of the emulsion or from another person were unsuccessful. The injections of skin emulsions into animals showed no evidence of active anaphylaxis to the proteins of the emulsions.

Stokes also made intradermal tests with a 0·5 per cent. suspension of agar in physiological salt solution. This suspension of agar produced in 2 normal individuals, who had not been taking potassium iodide, reactions like the luetin reaction. Intradermal injection of 20 per cent. suspension of bismuth subnitrate in salt solution in the same individual gave a slight reaction.

Stokes explains the reactions, such as those to normal skin, agar, luetin reactions in persons taking iodides, etc., as, in part at least, due to the introduction of antiferment adsorbents, the activity of which uncovers ferments normally present in the individual. He thinks that these proteoses split up the proteins of the body with the formation of anaphylatoxins, which in turn cause focal necrosis and inflammation. This explains the non-specificity of the cutaneous reactions. The agar skin reactions correspond to the anaphylaxis produced by agar, kaolin, and similar substances already described. **Stokes** points out " that the only value of such non-specific reactions from the clinical standpoint is to measure the enzyme balance or liability and the amount and intensity of action of non-specific proteoses in the body."

Similarly, **Hift** obtained intradermal reactions to colloidal silver preparations. These reactions never occurred on the first injection. These can be interpreted as the result of a disturbance of colloid equilibrium, the preparation acting as an adsorbent.

The question as to whether cutaneous reactions are an index of resistance or immunity has been frequently raised. **Kolmer** believes that there is no experimental support for the theory that allergic skin reactions may be taken as an index of resistance or immunity. Positive skin reactions do not run parallel with the presence of circulating antibodies; **Fleischner, Meyer,** and **Shaw** showed that guinea-pigs showing a high degree of acquired immunity to an organism, as evidenced by strongly positive agglutination and complement-fixation reactions and complete

resistance to a subsequent infection with living organisms, will never give specific positive cutaneous reactions. A state of anaphylactic hypersensitiveness can exist without the least cutaneous hypersensitiveness. As already mentioned, under the tuberculin reactions, cutaneous sensitiveness only occurs in the presence of infection. The mere injection of bacterial proteins will not produce skin sensitiveness. **Baldwin** confirmed this by placing in the abdominal cavity of guinea-pigs capsules of porous Berkefeld filter clay, some filled with living tubercle bacilli and others with filtered watery extracts of the tubercle bacillus. Cutaneous tests were negative on the 15th and 57th days afterwards. He therefore concluded that cutaneous hypersensitiveness does not develop through the mere presence of tubercle bacilli in the body, even although more or less accessible to the body fluids. Similarly, injections of the fatty or waxy substances in the tubercle bacilli and extracts of the bacilli themselves did not cause cutaneous hypersensitiveness.

Persons who have had typhoid fever or been inoculated against typhoid will react positively to paratyphoidin; yet it is known that these individuals are not immune to paratyphoid.

The cutaneous food reactions persist long after the patient ceases to have symptoms. The tuberculin Pirquet reaction persists for life even although the disease is apparently healed. The skin reaction in pneumonia often only appears after the crisis, when presumably immunity has been established. Therefore all the evidence goes to show that a positive cutaneous reaction is an indication of sensitiveness but not of immunity.

Another interesting point is the difference in the kind of reaction occurring in different conditions. Why is the reaction due to food proteins and drugs all over within almost three-quarters of an hour, whereas the tuberculin and similar reactions do not begin for 24 hours and persist for days? It cannot be a question of the degree of sensitiveness, otherwise they would all begin after the same interval, but some would last longer than others. It would point to there being some fundamental difference between the sensitisation which occurs in bacterial infections and that which occurs in food and drug sensitisations. The whole question of the cutaneous reactions requires further work before many points of importance can be clearly understood.

CHAPTER XVI

DESENSITISATION

Desensitisation or antianaphylaxis has already been discussed (p. 5) in its relation to anaphylaxis in general. Its importance in the treatment of disease requires that it be further dealt with from that point of view. Desensitisation may be specific or non-specific.

Specific desensitisation has already been fully described under the different diseases. It has been referred to in the prevention of serum sickness, in urticaria, drug rashes, plant dermatitis, food eczemas, etc. In each of these conditions the desensitisation is brought about by the injection or ingestion of the same substance which caused the sensitisation. Autogenous vaccine therapy in diseases where an organismal sensitisation occurs, such as in tubercle, certain forms of ringworm, gonorrhœa, etc., has also been mentioned under the different diseases.

Non-specific desensitisation, however, still requires to be dealt with. In it some substance either resembling or differing widely from that which caused the sensitisation is used. These substances may be roughly divided into 3 groups :

1. Non-specific protein desensitisers such as bacteria, peptone, milk, etc. ;
2. Auto- and hetero-serum ; and
3. Non-specific vaccines.

NON-SPECIFIC PROTEIN THERAPY

This method of treatment is also known as intravenous protein therapy, protein shock therapy, and pyrogenic therapy (**Auld**). Intravenous injection of foreign proteins gives rise to a fairly definite train of symptoms quite irrespective of the

protein injected. Many proteins have been used, chiefly bacterial emulsions, especially of the coli-typhoid group. Peptone, milk, auto- and hetero-sera have also been largely used.

A great deal of work has been done, especially in America, by injecting non-specific bacterial suspensions intravenously. It has been shown that the same results can be obtained by bacterial vaccines, *e.g.* bacillus typhosus or bacillus coli, in typhoid fever as by non-bacterial substances, such as normal serum, sodium nucleinate, and colloidal metals. The injection of these substances causes a febrile reaction (103°–104° F.) with a rigor which is thought to be essential if benefit is to result. If large doses are given nausea and vomiting may result. Before the rigor there is usually a leucopenia followed by a marked polymorphonuclear leucocytosis (about 40,000), reaching its maximum 2–12 hours after the rise of temperature. There seems to be no special relation between the degree of leucocytosis and the beneficial results following the injections. Most of the cases so treated were cases of typhoid fever and arthritis, but pneumonia, gonorrhœal complications, diphtheria, and sepsis were also treated. In typhoid fever cases the temperature falls by crisis after 2 or 3 injections. Similarly, the temperature in pneumonia may come down by crisis or lysis after a single injection of typhoid vaccine.

The reaction produced in these cases is known as the "protein shock reaction" and is independent of the vaccine used, *i.e.* it is not specific.

Kraus and **Mazza** found that they obtained the same results with intravenous injection of typhoid vaccine in both typhoid and paratyphoid and also with coli vaccines in typhoid. Numerous other observers lay stress on the non-specificity of the reaction. It is supposed to be due to the protein in the bacteria as distinct from the toxin. It acts by strengthening the defensive mechanism in the body. As **Williams** especially emphasises, in every specific infection there is probably a non-specific element due to the protein of the organism. The toxins are specific for each disease, but the protein sensitisation is the same in all, hence the symptoms common to all specific infections. **Miller** has shown that diphtheria can be successfully treated with normal horse serum if given early enough so as to counteract

the organism before it has had time to produce its toxin, and antidiphtheritic serum probably acts both by the antitoxin neutralising the toxin and the horse serum combating the diphtheria bacillus.

Davis and **Petersen**, by experiments on dogs with thoracic duct fistulæ, showed that recovery following protein shock therapy is due to changes in the lymph rather than the blood serum. There is an increase in the flow of lymph. Fluids rich in antibody are forced into the lymph channels. **Davis** and **Petersen** state that bacterial infections not confined to lymph spaces will not be influenced to the same effect by shock therapy. **De Castello** supports this view as he obtained a rapid fall of temperature by lysis or crisis in typhoid patients after the shock reaction, but injection of a similar dose of vaccine in typhus fever was without effect. **Davis** and **Petersen** also attribute the benefit of protein shock to the great increase in the antiferment which enters the circulation through the lymph stream. Bacteria proliferate best where the antiferment is absent, and after protein shock any increase in the antiferment would inhibit the growth of the invading organism.

Bull, in a series of experiments on rabbits, found that the intravenous injection of typhoid vaccine does not cause a specific stimulus. Unlike ordinary vaccine treatment, there is an immediate increase in antibodies. There is no preliminary negative phase. There is a rapid mobilisation of normal antibodies, thus increasing their concentration in the blood, to be followed later, as in other forms of inoculation, by the production of so-called acquired antibodies.

VACCINE PROTEIN SHOCK IN SKIN DISEASES

It is well known that certain skin diseases such as psoriasis, mycosis fungoides, and leprosy benefit by intercurrent infections in which a high temperature occurs. **Engman** and **M'Garry** employed intravenous injections of typhoid vaccine in doses of 75–500 millions. All cases showed a definite rise of temperature (100°–105° F.), and all showed a slight rise in the number of leucocytes after each injection. In all cases the skin lesion, especially in lupus erythematosus, became much redder and

sometimes itched for 1–3 hours after the injection, and herpes labialis was a common occurrence. Five cases of chronic psoriasis were treated. Injections, beginning with 100 millions, were given every 3 days. This caused the skin lesions to clear up, scaling diminished, and brown areas were left where the spots had been. But even in the most favourable cases relapses occurred in a short time.

Six cases of chronic lupus erythematosus were treated similarly. All were cases which had resisted numerous forms of treatment including X-rays and CO_2 snow. All improved markedly. A case of parapsoriasis was also markedly improved by the injections, and one of dermatitis herpetiformis to a slight degree. In a case of Darier's disease 1 injection stimulated the formation of new lesions. Cases of syphilis in various stages were treated, and in some, especially nodular lesions, the eruption disappeared and left pigmented areas. A case of acute exfoliative dermatitis showed great improvement.

Scully treated 8 cases of chronic psoriasis with intravenous injections of typhoid vaccine combined with suitable local treatment. After the 1st or 2nd injections the lesions became less inflammatory, but not smaller in size. When this was followed by the local application of chrysarobin ointment the lesions entirely disappeared in 8–16 days, *i.e.* much more rapidly than occurs in treatment with chrysarobin alone.

Sutton treated cases of psoriasis similarly. He used a mixed bacillus coli vaccine intravenously every 2–5 days simultaneously with the local application of 20 per cent. chrysarobin ointment. The disappearance of the eruption was very rapid usually—in 7 days on an average. **Capelli** and **Signorelli** used a cholera vaccine in physiological salt solution intravenously injected. Each case received only 1 injection, which was followed by a rise of temperature for a few hours. In a case of pemphigus vegetans the lesions showed a definite diminution for some days, followed by a slight recurrence of eruption. In 2 cases of pustular eczema there was a diminution of inflammation and suppuration, but an attack of influenza caused a recrudescence of the inflammation. In a case of lupoid sycosis the result was nil. In 4 cases of secondary syphilis a partial or complete resolution of the eruption took place. From all these results

therefore it is evident that by injection of non-specific bacterial emulsions an improvement in or disappearance of the eruption occurs in almost all the diseases treated. It would seem that a temporary desensitisation takes place, so that local treatment, as in psoriasis, has a much more rapid effect than usual. The improvement, however, seems to be only temporary, so that the method is on the whole of rather doubtful value except as an aid to local treatment.

TREATMENT OF OTHER DISEASES WITH INTRAVENOUS INJECTIONS OF VACCINE

Gow has found good results in the treatment of local streptococcal infections such as cellulitis with intravenous injections of a sensitised streptococcal vaccine. Similar good results were obtained in streptococcal septicæmia. Arthritis was also benefited by intravenous vaccine injections provided the treatment was given early in the case.

Paterson records marked improvement in a case of acute multiple arthritis from intravenous injections of typhoid vaccine. **Cecil** treated 40 cases of acute rheumatic, toxic, and gonorrhœal arthritis with a similar vaccine. The result was a rapid recovery in most of the rheumatic and toxic cases usually after 2 doses. The gonorrhœal cases were not much benefited. **Miller** and **Lusk** and **Cowie** and **Calhoun** also report good results in both acute and chronic arthritis.

Cowie and **Beavan** used a typhoid vaccine by intravenous injection in cases of influenzal pneumonia. It caused a termination of the acute symptoms in 1–3 days. The vaccine must be given before the 3rd day of the disease.

Miller and **Lusk** treated cases of typhoid fever with typhoid vaccine intravenously and obtained the same beneficial results as they obtained with albumose.

Roberts, Dudley, and **Carey,** in cases of influenzal pneumonia treated with intravenous injection of vaccine, had a mortality of 11·3 per cent. as compared with 31 per cent. in cases not so treated. **Squier** also reports astonishing and rapid improvements in 2 cases of influenza pneumonia from injection of typhoid vaccine. **Wells** similarly reports good results. **Ichikawa, Ludke,**

Rumpf and **Biedl** all record similar satisfactory results with intravenous vaccine therapy in typhoid fever. It did not matter whether the vaccine consisted of bacillus typhosus, bacillus coli, or bacillus pyocyaneus, the results being the same in all cases.

PEPTONE THERAPY

Peptone has been used extensively in the treatment of disease by intravenous injection in the same way as bacterial suspensions.

Schmidt and **Mulheim,** in 1880, were the first to study the effects of injecting digestion products such as peptone. **Fano** in the following year also worked on the subject. These observers noticed that injection of peptone caused an intoxication characterised by an alteration in the coagulability of the blood. **Brieger** thought the effect of the injections was due to production of a toxic substance which he called Peptotoxin. Similarly, **Pick** and **Spiro** considered the result due to a hypothetical substance which they called Peptozyme. But later, **Chittenden, Mendel** and **Henderson,** and **Underhill** and **Hendrix** showed that the previous workers had been using impure peptones, and that much of the result was due to the presence of proteoses.

In 1907 **De Waele** pointed out the striking analogy between the effects of peptone injections and anaphylaxis. **Vaughan's** work on the cleavage of protein in anaphylaxis seemed to support the suggestion that anaphylactic shock and peptone shock were the same thing. The work already described on agar intoxication by **Novy** and **De Kruif** showed the production of agar anaphylatoxin. By injecting guinea-pigs with peptone they showed that that substance produced the same effect as was produced by anaphylatoxin from agar and in specific anaphylactic shock. They found that the injections caused dyspnœa, spasms, convulsions, loss of control of the sphincters, low blood-pressure, death by stoppage of respiration, the heart continuing to beat for some time. They also claim that the post-mortem findings in peptone shock are the same as in typical anaphylactic shock, viz. distension of lungs, absence of clotting of the blood, etc. The lethal dose varied, the minimum being 0·5 grm. per kilo body weight. A certain immunity or tolerance is established after a non-fatal injection of peptone. Opinion is divided as to

whether the shock produced by peptone injections is identical with anaphylactic shock or not. Certainly there are many points of similarity between the two reactions. **Rusznyak** was the first to notice in protein shock a change in the antiferment in the serum. He concludes that, because in anaphylaxis the antitryptic power of the serum is enormously increased, "anaphylaxis is a condition produced by albuminoid substances which result from an abnormally rapid parenteral fermentation (peptone poisoning)." **Novy** agrees with the view, as he found that when normal serum is digested with Witte's peptone a toxic substance results which he believes to be identical with that which occurs in the body cells and fluids during anaphylactic shock.

Much work has been done on the blood changes in peptone shock. Fall of blood pressure, leucopenia, hyperviscosity, decrease of coagulability all occur as in anaphylaxis. **Brodin** and **Richet** did experiments to show whether peptone could prevent or attenuate anaphylactic shock. Dogs were sensitised to horse serum, and 1 hour before the toxogenic dose was given peptone was injected intravenously. This had the effect of causing only very slight symptoms, whereas in control animals where no peptone was given the animals showed very marked anaphylactic shock. **Larsen, Haigh, Alexander,** and **Paddock,** however, were not able to confirm this. **Bessau, Opitz,** and **Preusse** also, from their experiments on guinea-pigs, proved that, in doubly sensitised animals, antianaphylaxis, if produced, is a non-specific process as regards the antigens previously used. Similarly, the disappearance of precipitin from a serum was found to be non-specific. These results support the argument that peptone may act similarly to any antigen.

Weil has shown that if the normal liver of the dog be perfused with peptone solution it quickly presents the swelling and capillary congestion seen in anaphylactic shock in these animals. He does not think that anaphylactic shock is due to the production of peptonelike bodies in the circulation, but to a reaction on the sensitised liver cells, and so in peptone shock the effects are due to the change in the liver cells produced by the peptone. **Hisanobu** confirmed **Whipple** and **Van Slyke's** results, which showed that the injection of proteoses into the blood causes a great and rapid increase in autolysis of the body proteins,

resulting in a marked increase in urea-nitrogen and in non-urea- and amino-nitrogen in the blood serum. He found the changes in the nitrogen constituents of the blood in anaphylaxis to be similar to those in peptone intoxication, but more intense. Both anaphylaxis and peptone intoxication lead to an abnormally rapid autodigestion of tissue protein. The causative factors as yet undetermined are probably the same in both cases.

WHAT SUBSTANCE PRODUCES THE PEPTONE SHOCK ?

The question arises as to whether peptone shock is not due to the histamine which is present in commercial peptones and proteoses. Histamine shock has already been referred to (p. 13). **Hanke** and **Koessler** found that Witte's peptone contained not more than 0·00335 grm. in 100 grm. peptone. **Auld** calculates that this would mean that in an average dose of peptone (1 cc. of a 2 per cent. solution) there is $\frac{1}{1500}$ mgrm. of histamine. He found that this dilution gave a positive skin reaction in many persons, but intravenous injection of 0·3 cc. had either a very slight or negative effect. When this amount of histamine, however, was mixed with the usual doses of histamine-free peptone the injections gave the histamine effect in many persons (*i.e.* flushing, headache, salivation, palpitation, cyanosis, and dyspnœa). **Auld** therefore thinks that the peptone reinforces the action of the histamine. The intensity of the effect depends on the rapidity of injection. The reaction to histamine comes on at once and is not, like that of peptone, delayed for some hours, and is not associated with a rise of temperature. **Auld** states that histamine itself is quite useless in the immunising process, if not actually harmful. **Hanke** and **Koessler** found that histamine-free peptone produced the typical peptone shock.

The skin test can be used for the detection of histamine in peptone. All individuals gave a wheal reaction to histamine. If a peptone gives a marked reaction with the skin test, it probably contains histamine unless the patient is already sensitive to peptone. Intracutaneous tests to histamine are dangerous as they may lead to histamine shock. This is apt to occur if an intravenous injection is made soon afterwards. **Auld** therefore recommends Armour No. 2 peptone, which never gives the histamine effect.

Commercial peptones also contain numerous other bodies which may be the cause of symptoms on injection. As already shown, **Vaughan** found that heating of protein with alkali in alcohol produces a very toxic substance of the nature of a proteose. Pure peptone has very little toxic effect, and the effect of Witte's peptone on injection is chiefly due to the proteoses and albumoses in it. If peptone is heated with alkali or acid in alcohol a toxic substance like Vaughan's protein poison is produced. **Poplieski** called this substance Vaso-dilatin. **Clark** found by injecting mice that "1 grm. of Witte's peptone yielded 0·3 grm. vaso-dilatin, and that the minimum lethal dose of the peptone was 4 mgrm. per grm. of mouse, whilst the minimum lethal dose of the vaso-dilatin was 0·1 mgrm. per grm. From that he concludes that the vaso-dilatin cannot be preformed in the peptone, although it appears to be formed more readily from peptone than protein."

The effects produced by peptone, histamine, and other products of protein breakdown, as we have seen, are very similar, but they give different reactions in different species of animals, just as different effects are produced in different species of animals in true anaphylactic shock. These effects of protein shock in animals are shown by a rise of temperature with increased nitrogen metabolism, increased secretion of glands (*e.g.* salivation), contraction of non-striped muscles, and increased permeability of capillaries. Experiments on animals are not very satisfactory, firstly, from the differences in different species, and, secondly, because rabbits, guinea-pigs, rats, and mice are not very sensitive to protein shock. In human beings, however, treatment by the protein shock method has had considerable success. It has long been known that sudden absorption of products of breaking down tissues in the human body may lead to alarming symptoms. As an example, one may cite the rise of temperature and other symptoms of absorption seen by the too intensive X-raying of the tumours in mycosis fungoides. The patient may be poisoned by his own broken down tumours. There is also the evidence regarding traumatic shock which is apparently due to the breaking down of tissue protein. **Whipple** also showed that in acute intestinal obstruction the toxæmia is due to absorption of toxic proteoses.

TECHNIQUE

As **Gow** emphasises, intravenous injections of peptone in human beings must be made very slowly. A very fine needle should be used and someone should watch the pulse-rate. **Gow** recommends that the injection should be stopped temporarily if the pulse exceeds 35 beats per $\frac{1}{4}$ minute. The patient may complain of giddiness, pain in stomach, tickling in the throat, and may cough. These symptoms disappear almost immediately the injection is stopped. There is an immediate fall in blood pressure and the leucocytes disappear from the circulation into the pulmonary capillaries to appear later in increased numbers in the blood. The temperature should be taken 5 or 6 hours after the injection. There is often a rise up to 101° F. or over. **Auld** recommends the name pyrogenic therapy because of the temperature; but he advises that in the treatment of asthma, at first, a reaction should be avoided, and just sufficient dose given to get near the reaction point. He recommends that if the temperature rises 1° F. the next dose should not be increased. But if after 8 injections no improvement occurs, a larger dose should be given so as to produce a definite rise of temperature. In cases of asthma, which are very sensitive to peptone, **Auld** recommends the addition of a few drops of Lugol's iodine to the peptone. He usually begins with 5 m. (0·3 cc.) and gives injections twice a week, increasing each time by 0·2 cc. till 1·3 cc. (20 m.) is reached. This latter dose should be given 6 times, and the treatment continued for about 6 months, increasing the intervals between the injections later on.

There is some doubt as to whether a rise of temperature is an essential for successful treatment. Chronic conditions such as arthritis benefit most by a definite temperature reaction. **Auld** states that the effect of the pyrexia is—

1. Physico-chemical; and
2. Vital.

The former causes increase of enzyme action and of dissociation of absorption compounds. This leads to dissociation of oxy-hæmoglobin with a supply of more oxygen to the tissues. The

viscosity of the blood is reduced and its flow made easier and the dilatation of the blood vessels makes them more permeable to the serum. The vital changes are expressions of a marked stimulation of the reproductive capacity of certain cells. At first there is a leucopenia rapidly followed by a leucocytosis. Alterations in the leucocytes and blood pressure, phagocytosis of red cells by the large mononucleated cells of the blood, increase in blood platelets, in circulating antibodies, in non-protein nitrogen-content of the blood, in fibrinogen, globulin, thrombokenase, and blood sugar have also been described. Generally speaking, the injections cause, as **Clark** states, " a washing out of the tissue fluids into the blood and this process causes a number of changes in the composition of the blood." Unfortunately, the evidence at present is insufficient to indicate which of the changes observed is really of chief clinical importance.

THE KINDS OF PEPTONE USED

Auld recommends Armour's No. 2 peptone (5 per cent.) and Witte's peptone (2 per cent.). Witte's peptone contains primary and secondary proteoses in the relation of 1 to 2 ; whereas in Armour's No. 2 the proportion is only 1 to 7. **Auld** also uses a mixture of 3 parts of Witte's peptone and 5 parts of peptone practically devoid of primary proteose. Armour's No. 2 may also be used intramuscularly without causing irritation. Peptone siccum may be used, but requires the addition of some primary proteose. The solutions should be freshly prepared as they are then more active.

TREATMENT OF CASES WITH PEPTONE

In 1921 I treated 6 cases of skin disease with injections of Armour's No. 2 peptone (5 per cent.). It was prepared according to **Auld's** formula as follows :

Dissolve the peptone as far as possible by agitation in hot (56° C.) normal saline. Take the reaction to litmus (usually acid) and add *very carefully* normal or semi-normal sodium hydrate or carbonate until the solution is faintly yet distinctly alkaline to litmus. The peptone will now be dissolved except for some

insoluble residue. Make up to volume with normal saline and place in a water bath at 56° C. for half an hour. Filter while hot through ordinary filter paper and add to the filtrate 0·5 per cent. phenol.

If bottled, sealed rubber caps or well-fitting glass stoppers or rubber stoppers should be used. Wait for 3 days and then smear a loopful of the fluid on an agar slant and incubate for 16 hours at 37° C. If negative the peptone may be used.

The details of the cases treated are as follows:

Case 1. Prurigo (of Hebra)

H. W., female, age 18, unmarried. Admitted to Ward 2, Royal Infirmary, on 25th June 1921. A very typical case. Disease had lasted as long as patient could remember. Eruption worst on arms and legs, but a certain amount on face and body. Typical papular lesions, scaly and crusted. Very itchy; skin of limbs, especially extensor aspects, indurated and thickened. Glands in groins and axillæ enlarged and hard. Whole skin had pale pasty appearance. No history of asthma or bronchitis.

Family History.—Father and mother alive and well. Two sisters and 4 brothers. One sister dead—cause unknown. One brother had skin trouble in infancy. No history of asthma in family so far as known.

Skin Tests to Food Extracts.—June 28, 1921 (see also under Cutaneous Tests).—Tests were done on anterior aspect of left arm.

Results.—*Negative* to cow's milk, oatmeal, pea, pork, potato, haddock, wheat, herring, lamb, lentil, cabbage, cocoa, bean, beef, tea.

Positive (lasting over 1¼ hour) to salmon, egg white, egg yolk, and chicken.

Doubtful (lasting less than 1 hour and not so marked reaction as above) to veal, carrot, cheese, and barley.

Patient was given later salmon (tinned), eggs, and chicken, veal, carrot, cheese, and barley to eat, but in no case was the eruption affected one way or another.

July 12, 1921. Unbroken skin of chest rubbed with white and yolk of raw fresh egg on different places and although left in

contact with skin for some hours no reaction produced. Skin of right forearm also rubbed with some of patient's own blood, but with no effect.

July 12, 1921. 5 minims peptone (Armour's) solution (5 per cent.), intravenous, right wrist.
,, 16. ,, 8 minims peptone (Armour's) solution (5 per cent.), intravenous, right wrist.
,, 19. ,, 11 minims peptone (Armour's) solution (5 per cent.), intravenous, right wrist.
,, 23. ,, 14 minims peptone (Armour's) solution (5 per cent.), intravenous, right wrist.
,, 26. ,, 17 minims peptone (Armour's) solution (5 per cent.), intravenous, right wrist.
,, 30. ,, 20 minims peptone (Armour's) solution (5 per cent.), intravenous, right wrist.

Aug. 2, 6, 9, 13, 16, and 20, patient received similarly 20 minims peptone solution.

All injections were given into vein in front of right or left wrist, as it was impossible to find any vein in front of elbow owing to smallness of the vessels and thickening of the skin.

The injections caused no local irritation or reaction even although, when the 3rd injection was given, some of the peptone solution escaped into the subcutaneous tissues.

On July 19 (*i.e.* after 2 injections) skin test done with peptone solution on right forearm. Result negative.

The temperature was taken 4-hourly for 24 hours after each injection, but at no time showed any alteration from normal. No symptoms of any kind occurred after any of the injections. The skin eruption did not seem to vary after injection nor was there any definite effect on the itching. No rise of temperature after injections. Locally the skin was treated with a daily warm bath and the application of plain vaseline, and later 1 per cent. ichthyol paste.

Patient had an ordinary diet and internally Parrish's syrup, 3i. t.i.d. Whilst under treatment the eruption gradually became less, and when patient left hospital on 20th July there were only a very few isolated papules to be seen here and there on arms and legs. The face and body were free of eruption.

The skin, however, still remained thickened and indurated. Patient was given 1 per cent. ichthyol paste to apply at home. During stay in hospital her weight increased from 5 st. 12½ lbs. to 6 st. 6½ lbs.

Result.—Very much the same as would have occurred had no peptone been given.

Case 2. Dermatitis

K. M., male, age 59. Occupation—diver. Patient was first seen in December 1920 with a dermatitis of face, neck, arms, and groins of 2 months' duration. He was seen at intervals, and on 20th September 1921 he was admitted to Ward 2, Royal Infirmary, under Sir Norman Walker. On admission, the face, neck, arms, and groins were the seat of a very scratched dermatitis. The skin was indurated, leathery, and wrinkled, especially on forehead and round eyes. The itching was intense. The general appearance of the dermatitis suggested at first a dermatitis venenata. He had been working with plaster making a cast of dock gates; but stopping work had no effect on the dermatitis. He had marked arterio-sclerosis.

Oct. 8, 1921. Peptone (intravenously) 5 m. into right arm.
„ 11, „ „ „ 8 m. „ „ „

Eruption gradually spreading, but the spread had begun before he was given the injections.

Oct. 15, 1921.	Peptone Pirquet	±	Peptone 11 m.
„ 18, „	„ „	—	„ 14 m.
„ 21, „	„ „	—	„ 17 m.
„ 25, „	Peptone 20 m.		Itching worse for 2 nights after this injection.
„ 29, „	Peptone 20 m.		
Nov. 1, „	„ 20 m.		
„ 5, „	„ 20 m.		Skin less scratched.
„ 8, „	„ 20 m.		Skin improved.

Injections stopped as patient was not feeling well. No rise of temperature after injections. Whilst injections were being given he was treated successively with starch poultices, calamine lotion, weak tar lotion, ammoniated mercury paste 1 per cent., and mercury and carbolic ointment.

Result.—Improved, but no more than would be accounted for by rest in bed and local treatment.

Case 3. Furunculosis and Sycosis

D. K., age 25. Admitted to Ward 2 on 1st July 1921 with a marked sycosis of upper lip and beard region. The area was very red, swollen, and pustular. On axillæ, pubic regions, and thighs a series of papulo-vesicular lesions were present. His complaint began 5 years ago. Has had furuncles off and on for many years. Has had vaccine inoculations 6 times; was X-rayed twice, and hair brought out with temporary improvement only. Wassermann reaction negative.

July 16, 1921. Peptone (intravenously) 5 m. right arm.
„ 19, „ „ „ 8 m. „ „
„ 23, „ „ „ 11 m. „ „

This injection was followed about 8 hours later by a reaction in the skin. The whole skin became very itchy, especially on the left axilla and pubic region. The face lesions became very red and remained so for 2 days or so.

July 27, 1921. Peptone 11 m. Peptone Pirquet slight +.
„ 30, „ Peptone 11 m. Skin very much better in all areas. Patient thought his skin was better than it had been for years.
Aug. 2, „ Peptone 14 m. This injection made the eruption worse.
„ 6, „ Peptone 11 m.
„ 9, „ „ 11 m. Skin slightly improved.
„ 13, „ „ 14 m. This was followed by an increase in the itching.
„ 16, „ Peptone 8 m.

No rise of temperature occurred after any of the injections. Starch poultices and 1 per cent. ammoniated mercury paste were applied locally to the lesions.

Result.—Reaction in the skin after injections. At first eruption worse, later increased itching after each injection. Improved considerably on the whole. Patient left the ward suddenly without leave and has not been seen since.

Case 4. Psoriasis Vulgaris

J. R., female, age 15. Psoriasis vulgaris.

History.—Treated for psoriasis in skin wards from January to May 1918. At that time had an acute nephritis from which she made a good recovery. Psoriasis cured when she left the hospital in May 1918. Fresh outbreak of psoriasis in February 1919. Readmitted to ward and discharged almost well on 6th May 1919, after treatment with 1 per cent. sulphur salicylic ointment and strong chrysarobin, salicylic, and carbolic ointment on legs. She remained much the same for 4 months when psoriasis returned again.

There is a history of psoriasis in the paternal grandmother.

Oct. 8, 1921. Patient shows an extensive psoriasis of scalp, body and limbs. Most of the lesions in fairly large patches of usual appearance.
„ 8, „ Peptone (intravenous) right forearm 5 m.
„ 11, „ „ „ „ „ 8 m.

Temperature rose the same evening to 100·8° F. and fell to normal next day.

Oct. 15, 1921. Peptone Pirquet definitely+. Peptone (intravenous) 5 m. No temperature.
„ 18, „ Peptone Pirquet again+. Peptone (intravenous) 8 m.
„ 21, „ Peptone (intravenous) 11 m. Peptone Pirquet negative. No temperature. Patient vomited the same evening. Fresh spots of psoriasis appearing.
„ 25, „ Peptone (intravenous) 11 m. Vomited the same evening. Psoriasis spreading.
„ 29, „ Peptone (intravenous) 14 m. No sickness. Old spots of psoriasis have all faded. Fresh eruption no longer spreading.
Nov. 1, „ Peptone (intravenous) 17 m. No reaction.
„ 5, „ „ „ 20 m. „ „

Whilst the injections were being given local treatment was carried on with a daily sulphur bath, oil of sesame, and later 1 per cent. and 2 per cent. sulphur salicylic ointment.

Result.—Disappointing. Did not improve any more quickly than if no injections had been given and fresh eruption came out during the injections. Rise of temperature after 2nd injection. Vomiting after 4th–5th injections.

Case 5. Psoriasis Vulgaris

J. H., female, age 9 years. Psoriasis of 18 months' duration. Numerous small lesions scattered all over body and limbs.

Sept. 6, 1921. Admitted to ward. Treated with daily sulphur bath and 1 per cent. sulphur salicylic ointment.
Oct. 8, ,, Very little improvement. Peptone (intravenous) 5 m.
,, 11, ,, Peptone (intravenous) 8 m.
,, 15, ,, ,, ,, 8 m.
,, 18, ,, ,, ,, 11 m.
,, 21, ,, ,, ,, 14 m. Peptone Pirquet negative. Small new spots of psoriasis coming out on body and limbs.
,, 25, ,, Peptone (intravenous) 14 m.
,, 29, ,, ,, ,, 17 m. No change in eruption.

Local treatment with sulphur baths and sulphur salicylic ointment continued whilst injections were being given. No rise of temperature or other reaction occurred after any of the injections.

Result.—Disappointing. As in Case 4, no more rapid result than would have occurred had no peptone been given. Fresh spots appeared during the course of the injections.

Case 6. Psoriasis Vulgaris

J. M'E., female, age 17 years. Large patches of psoriasis on scalp and trunk of 7 years' duration.

Oct. 11, 1921. Peptone (intravenous) 5 m.
,, 15, ,, ,, ,, 8 m. Peptone Pirquet negative.
,, 18, ,, Peptone (intravenous) 11 m. Peptone Pirquet negative.

Oct. 21, 1921. Peptone (intravenous) 14 m. Peptone Pirquet negative. Psoriasis in *statu quo.*
„ 25, „ Peptone (intravenous) 17 m.
Nov. 1, „ „ „ 20 m.

No temperature or other reaction occurred after any of the injections.

Whilst having the injections, local treatment was carried out with 2 per cent. sulphur salicylic ointment. As soon as injections were stopped patient was put, on 2nd November, on chrysarobin vaseline 4 per cent. for the body and 4 per cent. sulphur salicylic ointment for the scalp. The chrysarobin ointment caused a very severe and immediate reaction, and 2 days later (4th November) the temperature rose to 101·6° F. Chrysarobin zinc paste (2 per cent.) was substituted for the 4 per cent. ointment and the temperature fell next day. Patient left the ward cured on 1st December.

Result.—Injections had no effect at the time, but subsequent application of chrysarobin produced a much more rapid and severe reaction than usual.

Discussion of Cases

Six cases of skin diseases were treated with injections of peptone given intravenously, beginning with 5 m. of a 5 per cent. solution and gradually increasing to 20 m. In only 1 case was there any rise of temperature after the injection, and in the same case vomiting occurred twice. In Case 3 the eruption was made worse at first and the itching was increased, but improvement set in later. Apart from these cases the injections caused no disturbance whatever. Of the 6 cases, 1 suffered from prurigo, 1 from a fairly extensive dermatitis, 1 from furunculosis and sycosis, and 3 from psoriasis.

The cases of prurigo and of dermatitis did not improve any more than all such cases do with hospital treatment. The case of furunculosis and sycosis improved somewhat, and the cases of psoriasis were not affected, except that in 1 the subsequent use of chrysarobin caused a more severe reaction than normal. On the whole, the results were so disappointing that the method was given up.

I have only been able to find 2 other references to the use of injections of peptone in skin diseases. **Von Alstyne** treated 4 cases of psoriasis with injections of an alkaline mixture of proteoses and peptones. They caused no reaction and the eruption disappeared in some weeks without local treatment. **Ambrosoli** used Armour's peptone (5–10 per cent.), giving it intramuscularly twice a week, and Merck's deutero-albumose (2–5 per cent.), given intravenously. Practically no result was obtained in cases of eczema, lichen, and dermatitis herpetiformis. Peptone has been given successfully by **Pagniez** and **Vallery-Radot** by the mouth in cases of urticaria. They found that in cases of urticaria due to eggs, shell-fish, etc., a small amount of the offending protein taken half an hour before a meal would prevent symptoms. A tablet of 0·4 or 0·5 grm. peptone similarly taken before the meal had the same effect. The continuous use of the peptone for some time cured the condition. They also quote a case of **Ramond's** of general pruritus in a female, which was cured by the ingestion of peptone. **Joltrain** records 3 cases, 2 of urticaria and 1 of asthma, due to eating eggs or other food, which were completely cured by taking peptone before meals. I have tried this method in a few cases of chronic dermatitis, but without any beneficial result.

RESULTS IN OTHER DISEASES

Auld has obtained good results in the treatment of asthma with peptone injections. He found the most suitable cases were those who showed intervals when they were free of bronchitis and who had not much emphysema. Cases of continuous asthma did not do well, possibly because the anti-anaphylactic mechanism had broken down. This might also account for the lack of result in chronic skin diseases. **Auld** also records a good result in a case of recurrent migraine with injections of peptone, and **Pagniez** and **Vallery-Radot** report a cure in 5 cases of migraine from the administration of 0·5 grm. peptone by the mouth half an hour before meals.

Nolf obtained satisfactory results in the treatment of typhoid fever, strepto- and staphylo-coccal septicæmias with injections of a 10 per cent. solution of peptone. He also found this method

efficaceous in obstinate cases of acute rheumatism combined with salicylate treatment.

Matthes studied the effect of injection of deutero-albumose and peptone as compared with tuberculin in tuberculosis, and came to the conclusion that the effect of the tuberculin was the same as that produced by these substances.

From a study of all these cases the best results from the use of peptone, therefore, seem to have been obtained in asthma. Whether the results are permanent is open to doubt. I have seen 1 case of asthma which benefited greatly at the time, but relapsed some months later. In skin diseases the results with peptone on the whole are disappointing.

MILK THERAPY

As the results were so disappointing with peptone injections, I tried the effect of intramuscular injections of sterilised milk in various skin diseases.

The effect of milk injections is very much the same as that of intravenous vaccine. A form of shock is produced resulting in a rise of temperature some hours later and a marked leucocytosis. Up to the present 11 cases have been so treated. Details of these cases are as follows:

Case 1. Dermatitis

B. B., male, age 40 years. The patient was first seen on 7th November 1921. He had a history of eczema in infancy. Eight years ago he had a slight recurrence of the eczema lasting about a month. This attack began about 6 months before he was seen. In November 1921 he had an extensive itching dermatitis of scalp, face, neck, axillæ, arms, upper part of body, and behind knees. Food tests to all the common foods were negative. As he was no better in March 1922 milk injections were given to the patient in bed in a nursing home.

Mar. 22, 1922. Injection 2·5 cc. boiled milk into right buttock, followed by no reaction.

„ 25, „ Injection 5 cc. boiled milk into left buttock. This was followed by a temperature of 101·4° F. for some hours.

Mar. 28, 1922. Injection 5 cc. boiled milk into right buttock, followed by rise of temperature to 99·5° F.
Apr. 1, ,, Injection 6 cc. boiled milk into left buttock.

Almost immediately afterwards he complained of a constricted feeling round the chest and fluttering of the heart. The pulse was regular. He was slightly cyanosed and had a short cough such as occurs in pneumonia. I immediately injected 3 minims adrenalin (1–1000) hypodermically. This produced no result. The cough and constricted feeling in chest lasted about 20 minutes when the symptoms gradually subsided, and in an hour he felt quite well again. This attack was evidently not an asthmatic one, but a fat embolus due to some of the milk getting direct into a vein and blocking some of the vessels in the lung temporarily. Whilst having the injections he was kept in bed and treated with 1 per cent. ichthyol paste and 1 per cent. tar paste. The eruption improved very much.

Result.—Satisfactory. He left the home on 13th April, and on 27th April reported that the skin was well.

Case 2. Dermatitis Seborrhœica

J. J. C., male, age 26 years.

This was a private case sent to me by Dr. Gibson. He showed a typical seborrhœic dermatitis of scalp, face, neck, and flexures of elbows. As dieting and removal of septic teeth had no effect and local treatment only caused a temporary improvement, 2 years after he was first seen I recommended boiled milk injections. Dr. Gibson gave him 5 injections at 3-day intervals in doses of 2·5, 5·0, 7·5, 7·5, and 7·5 cc. None of the injections caused any rise of temperature. The skin eruption became worse after the 4th injection, and after the 5th injection he complained of a severe shooting pain in the small of the back which lasted for a few minutes.

Result.—Disappointing. He improved slightly, but not more than could be accounted for by the rest in bed.

Case 3. Dermatitis Seborrhœica

A. F., male, age 55 years.

This patient was first seen in January 1921, with a seborrhœic

dermatitis of scalp, ears, neck, axillæ, fronts of elbows, backs of arms, behind knees, groins, and genitals. This patient was tested to all the common foods, but gave no reaction to anything. He was an alcoholic, and nearly every local application except lanolin caused irritation. He improved and relapsed for about a year, when milk injections were given.

Mar. 4, 1922. Injection 2·5 cc. boiled milk into right buttock.
„ 7, „ „ 5 cc. „ „ „ left „
„ 10, „ „ 7·5 cc. „ „ „ right „

Each injection was followed by a temperature of about 99° F. The injections were stopped as he complained of pains all over and a feeling of general malaise.

Result.—Nil.

Case 4. Neuro-Dermatitis

J. P., male, age 54 years.

This patient had suffered from asthma for years. The asthma suddenly stopped about 4 months before he was seen. As soon as the asthma stopped a general itching of the skin began. Scratching led to the production of a dermatitis, and when seen on 11th March 1922 he had a general itching all over the skin, which was scratched, red, scaly and indurated. There was also a general sweating of the skin. Milk injections were recommended and he was given 6 bi-weekly injections of boiled milk by Dr. Pratt of Whitehaven. As there was a history of asthma the first dose was 1 cc., which was increased gradually to 10 cc. These were not followed by any rise of temperature, but there was a very slight return of the asthma.

Result.—The injections had very little effect on the itching and the dermatitis. Dr. Pratt reported "perhaps a slight improvement."

Case 5. Xantho-erythrodermia Perstans

G. S., male, age 53 years.

This patient showed large areas of bluish-red eruption affecting the skin of the body and limbs. It corresponded very closely to the condition described by **Crocker** as xantho-erythrodermia

perstans. He had been in numerous hospitals during the last few years, and all kinds of treatment had been used without improvement. He was admitted to the skin wards on 27th January 1922. X-rays and Finsen light were tried but had no effect.

Feb. 11, 1922. Injection boiled milk 2·5 cc. into right buttock.
„ 14, „ „ „ „ 5 cc. „ left „
„ 18, „ „ „ „ 5 cc. „ right „
„ 21, „ „ „ „ 7·5 cc. „ left „
Injection given at 12 noon.
Leucocyte count at 2 p.m. 9,600.
„ „ „ 5 p.m. 11,200.
„ 22, „ „ „ „ 10 a.m. 5,600.
„ 25, „ Injection boiled milk 10 cc. into right buttock.
„ 28, „ Leucocyte count at 10 a.m. 7,800.
12 noon. Injection boiled milk 10 cc. into left buttock.
1 p.m. Leucocyte count 8,400.
3 p.m. „ „ 11,200.
5 p.m. „ „ 10,400.
Mar. 4, „ Injection boiled milk 10 cc. into right buttock.
„ 7, „ „ „ „ 10 cc. „ left „

Each injection was followed by a slight rise of temperature for 8–12 hours, 100·6° F. being the highest. When the blood was examined before and after each injection a marked leucocytosis was present after the injection.

Result.—Absolutely nil as regards the effect on the skin eruption.

Case 6. Psoriasis and Dermatitis Exfoliativa

Mrs S., age 50 years. Patient was admitted to ward on 19th October 1921 with psoriasis on scalp, flexor aspects of both forearms, sacral region, and legs. Before admission the eruption was spreading. At first patient was treated with 2 per cent. sulphur salicylic vaseline on the scalp and plain vaseline on body and limbs. Internally thyroid gr. ii night and morning was administered till 22nd November, then vin. antimoniale m. iii t.i.d. was given till 12th December, when quin. sulph. gr. ii was

substituted. During that time the eruption changed in character, becoming much redder and spreading all over the body and limbs till by the beginning of December the patient showed the eruption of a typical exfoliative dermatitis (pityriasis rubra). The eruption covered the whole of the skin except the central part of the face, the fingers and toes, and the palms and soles. During the spread of the eruption the temperature, which was 98° F. every morning, went up every night usually to about 100°, but on 2 occasions it was 101° F. When the eruption stopped spreading the temperature slowly came down almost to normal. After the eruption had been stationary for about 6 weeks, on 5th January 1922 treatment with milk injections was commenced.

Jan. 5, 1922. Injection 2·5 cc. boiled milk intramuscularly into right buttock. The injection caused no local pain or discomfort. No effect on temperature.

,, 10, ,, Eruption distinctly better. Distinct areas of paler skin beginning to appear. Injection 5 cc. boiled milk into left buttock. No rise of temperature.

,, 17, ,, Eruption still becoming paler. Injection 5 cc. boiled milk into right buttock.

,, 21, ,, Injection 10 cc. boiled milk into left buttock.

,, 24, ,, ,, 10 cc. ,, ,, ,, right ,,

,, 28, ,, ,, 10 cc. ,, ,, ,, left ,,

Exfoliative eruption has almost entirely disappeared. Psoriasis spots still visible.

Jan. 31, 1922. Injection 10 cc. boiled milk into right buttock. Skin now shows no sign of exfoliative dermatitis, but small psoriasis spots have appeared here and there on body and limbs.

Feb. 4, ,, Injection 10 cc. boiled milk into left buttock. Injections were then stopped. Under 1 per cent. ichthyol paste the psoriasis spots rapidly subsided, and on 18th February patient was discharged absolutely cured.

Result.—Most satisfactory. The exfoliative dermatitis began to improve immediately after the 1st injection. Eight injections

were given, and by the time the 6th injection had been given (*i.e.* in about 3 weeks) the exfoliative dermatitis had entirely disappeared. The injections did not have the same immediate effect on the psoriasis, but with mild local treatment after the injections were stopped the psoriasis disappeared much more rapidly than usual. None of the injections caused any pain or discomfort, and no temperature or other reaction was seen.

Case 7. Dermatitis Exfoliativa Generalisata

C. J., age 60, was admitted to the skin ward on 30th March 1921 suffering from a dermatitis of face, neck, arms, groins, and thighs; very itchy. Treated with tar paste, ichthyol paste, liquor alumin. acetate, etc. No treatment had much effect. He left the ward on 26th June, still having a very red, cracked dermatitis of arms, groin, scrotum, and inside of thighs. He was seen by Sir Norman Walker in Chalmers Hospital on 12th October, when he showed the clinical picture of a general exfoliative dermatitis. He was transferred later to the Longmore Hospital for Incurables. There he received boiled milk injections in doses of 2·5, 5·0, 7·5, 5·0, 7·5, and 7·5 cc. twice a week. He had a rise of temperature after each injection. The injections had no effect on the eruption, but his general condition was never good. He suffered from marked arterio-sclerosis, and died some months later. Some months before death he became very thin and the skin showed a marked brown pigmentation suggestive of Addison's disease.

Case 8. Dermatitis Exfoliativa Generalisata

W. M., male, age 64 years.

Patient was first seen on 23rd November 1922 with a typical red, dry, scaly exfoliative dermatitis all over head, face, trunk, and limbs. The eruption began on the hands and feet and gradually spread till the whole body was affected. Milk injections were suggested and Dr. Maclagan of Ayton gave them. Six injections of boiled milk at intervals of 3 days beginning with 2·5 cc. and ending with 10 cc. were given. These caused a diminution in the redness of the skin and a marked diminution in itching. He was seen again in April 1923, when the slight improvement

was maintained, but the skin, though paler, was still red and scaly all over. There was no reaction of any kind after the injections.

Case 9. Dermatitis Exfoliativa Generalisata

A. S., male, age 40.

The eruption began as a dermatitis on the legs about a year ago and gradually spread all over till the whole skin was affected, showing a general exfoliative dermatitis of the seborrhœic type. There was a good deal of itching. Milk injections were recommended and given by Dr. Heron, Markinch. He had 8 injections of boiled milk beginning with 2·5 cc. and gradually increasing up to 10 cc. The result was disappointing as no improvement took place.

Case 10. Dermatitis Exfoliativa

J. R., male, age 33 years.

Admitted to Ward 1, Royal Infirmary, 6th September 1923. His skin eruption began 9 years ago on the hands, evidently as a dermatitis. He suffered off and on from a dermatitis of hands and arms, with intervals of freedom from eruption till September 1922. At that time the soles of the feet became affected. The eruption disappeared and reappeared in January 1923 on hands and feet, gradually spreading up on to the limbs and body, and when admitted in September the whole skin was affected except the upper parts of face and chest. The eruption was bright red and scaly all over, with an abrupt edge. The patient was treated with a daily sulphur bath. A half per cent. sulphur salicylic ointment was applied to the scalp and a paste of zinc oxide and liquid paraffin to the body and limbs. The latter was replaced later by cold cream. Salicin gr. x. t.i.d. was given internally.

Nov. 14, 1923. Blood sugar, 114 mgrm. per cent. Blood pressure $\frac{118}{80}$.

,, 15, ,, Injection sterilised milk (intramuscular), 2·5 cc. Leucocyte count 2 hours later was 13,430. Temperature on same night, 99·2° F.

Nov. 19, 1923. Injection sterilised milk, 5 cc. Leucocytes 2 hours later, 8,125. Temperature same night, 100° F.

„ 22, „ Injection sterilised milk, 7·5 cc. Temperature same night, 101·6° F.

„ 26, „ Injection sterilised milk, 5 cc. Temperature same night, 101·4°. During the night the patient was very restless with slight delirium. The skin slightly paler especially on the back.

„ 29, „ Injection sterilised milk, 2·5 cc. Temperature same night, 99° F.

Result.—Skin slightly paler all over. Improvement most marked on head and upper part of back.

Case 11. Psoriasis

Mrs R., age 55 years.

This patient was first seen in 1915 with a psoriasis of scalp and limbs of 4 years' duration and of rather an inflamed type. She was treated in a nursing home with sulphur salicylic ointment in increasing strengths and crude coal tar latterly, and the eruption disappeared in about 8 weeks. The eruption recurred about 6 weeks later. She was again treated similarly in bed with the addition of X-rays to the more resistant areas. She relapsed again some months later and had a course of sea-water plasma injections subcutaneously. She improved and went to Harrogate where she had a course of sulphur-bath treatment. During the next 6 years she was never quite free of eruption, so a course of milk injections was recommended in addition to local treatment with 1 per cent. sulphur salicylic ointment and crude coal tar.

July 29, 1922. Injection 2·5 cc. boiled milk into right buttock.
Aug. 1, „ „ 5 cc. „ „ „ left „
„ 4, „ „ 5 cc. „ „ „ right „
„ 8, „ „ 6 cc. „ „ „ left „
„ 11, „ „ 7·5 cc. „ „ „ right „
„ 15, „ „ 10 cc. „ „ „ left „

There was no rise of temperature after the injections except after the 3rd injection (99·5° F.). She complained of a feeling

of general discomfort and nervousness for about 48 hours after each injection

Result.—The psoriasis lesions became paler, but did not disappear. On the whole, a disappointing result. She relapsed later and is still uncured. The injections apparently had no effect in accelerating the effect of local treatment.

Briefly summarised, 11 cases of skin disease have been treated with milk injections. The cases were dermatitis (1), seborrhœic dermatitis (2), neuro-dermatitis (1), xantho-erythrodermia perstans (1), dermatitis exfoliativa (5), and psoriasis (1).

TECHNIQUE

In all cases ordinary fresh dairy milk was used. The injections were made as early in the forenoon as possible, because it is important that the milk should be used before many bacteria have had time to multiply in it. Some of those, who have used this method, state that the rise of temperature following the injections does not occur if the milk is absolutely fresh. **Ford** has shown that bacillus Welchii, growing in milk, gives rise to toxic products which, if injected into rabbits and guinea-pigs, can produce sudden death. The result is due to toxins produced by the bacteria, because the same results are obtained when the bacteria themselves are removed by filtration. It is not necessary to get the milk in specially sterilised vessels. I found that fresh morning's milk was quite suitable up to 11 o'clock in the forenoon. A small jam jar (which holds $\frac{1}{2}$ lb.) is half filled with milk and a teaspoon is placed in it. This is placed in a pan of hot water and covered with a lid. The water in the pan is then boiled for 15 minutes. The jam jar is taken out and the " skin " removed from the top of the milk by the teaspoon. A large Record syringe with a long needle of large bore is filled with the milk, which is injected deeply into the gluteal muscle in the usual way. Care should be taken that the milk is not injected direct into a vein, otherwise a fat embolism is produced as occurred in Case 1. If the piston is withdrawn slightly before injecting and no blood comes into the syringe, it is quite safe to give the injection. For adults the first dose is 2·5 cc., then 5 cc., 7·5 cc., and 10 cc., the last being repeated several times if necessary. For children smaller doses should be given, 1 cc. at first, increasing by 1 cc.

till 5 cc. are reached. Injections are given twice a week into right and left buttock alternately. The injections should be given slowly and the patient kept in bed. The method is contra-indicated in milk asthmatics.

RESULTS IN MY CASES

One case of chronic more or less generalised dermatitis of unknown origin did extremely well. He had 4 injections with a rise of temperature after 3 of them. This case had milk embolism after the last injection, but made a good recovery. In 2 cases of seborrhœic dermatitis, in one there was slight improvement, in the other the result was nil. In 1 case of neuro-dermatitis (general pruritus) in an asthmatic the result was disappointing, both as regards the effect on the itching and the dermatitis. One case with an eruption corresponding to what **Crocker** described as xantho-erythrodermia perstans had 8 injections with no result. Five cases of exfoliative dermatitis were treated. In 1 the result was astonishingly good, improvement beginning after the 1st injection. I think the result must be attributed to the injections, as these cases are notoriously slow and unresponsive to treatment. After the exfoliative dermatitis disappeared, the psoriasis, which had been previously present, remained, but it too responded more readily to local treatment than normal. In the other 4 cases of exfoliative dermatitis 2 improved slightly, but the result was negative in the other 2 cases. In the 1 case of psoriasis treated, the result was disappointing.

In nearly all cases a slight rise of temperature occurred after each injection, and if above 100° F. the dose of the next injection was not increased. Apart from the fat embolism already mentioned, no alarming symptoms were produced. One case was slightly delirious with a temperature of 101·4° F., and another case complained of malaise and nervousness for 2 days after each injection. In all cases where the blood was counted there was a marked leucocytosis 3–5 hours after the injection. The results, therefore, on the whole are encouraging, and the method seems worthy of more extended trial, especially in exfoliative dermatitis and similar conditions which do not yield well to any known treatment.

RESULTS OBTAINED WITH MILK INJECTIONS IN SKIN DISEASES BY OTHER WORKERS

Ambrosoli had the same experience as I had. After trying peptone injections and finding the results disappointing, he gave them up in favour of milk injections. He reports good results in 2 cases of eczema of nipple, 1 of chronic eczema of scalp and flexures, 3 cases of seborrhœic dermatitis, and 2 cases of eczema in babies. He obtained improvement in a case of lichen planus, but no result in 4 cases of psoriasis. A case of chronic pemphigus was benefited and a case of furunculosis was cured after 2 injections. **Morini** treated 12 cases of soft sore and buboes. The milk injections acted very beneficially on the buboes but had no effect on the soft sores. **Cattaneo** also obtained exactly similar results. **Guszman, Antoni,** and **Berndt,** on the other hand, report a good effect on the soft sores themselves. **Ahlsmede** recommends the injection of a germ- and toxin-free solution of milk albumin in all local and general staphylococcal skin lesions (furunculosis, carbuncles, pyodermia, etc.), in superficial and deep trichophytosis in buboes, and gonorrhœal complications. **Müller** obtained satisfactory results in sycosis, impetigo contagiosa, soft sore, and gonorrhœal complications. He puts the effect of the injections down to the leucocytosis and not to the rise of temperature, which does not occur if the milk is not infected.

Gawalowski used a modified form of treatment. He gave intracutaneous injections of a milk preparation called Lactin. Sixteen cases of deep tinea barbæ were healed with good result, but cases of staphylococcal sycosis were not benefited. **Kruger** and **Pfeiler** report the result of treating animals suffering from skin diseases with subcutaneous injections of Yatren, a protein similar to that obtained from casein. He obtained cures in alopecia areata in a dog, 2 cases of tinea in dogs, dorsal eczema with alopecia and furunculosis in a dog, itchy eczema in a horse, and eczema in a pig. **Varney** obtained marked improvement in cases of infantile eczema as the result of giving a small rectal injection of cow's milk every 2–3 days. The first effect was a marked aggravation of the eruption within 24 hours, but rapid improvement soon occurred in 50 per cent. of the cases.

MILK INJECTIONS IN OTHER DISEASES

Müller and **Thanner** used milk injections with success in arthritis, conjunctivitis, and iritis, **Friedländer** in trachoma, and **Uddgren** in parenchymatous keratitis. **Schmidt** also treated cases of arthritis with milk injections, and **Schmidt** and **Saxl** obtained good results in cases of typhoid fever. **Ziembowski** found the method good in cases of sepsis and tuberculosis, especially of bone. **Levi** found improvement in 3 cases of vomiting of pregnancy after a course of milk injections. The method is still on its trial, but is one which might be tried in many conditions where a sensitisation of unknown cause is probably present. With ordinary care there is no risk from the injections.

AUTO- AND HETERO-SERUM THERAPY OF SKIN DISEASES

That homologous and heterologous normal blood has toxic properties was demonstrated by the accidents which occurred when transfusion of blood was performed in the early days of surgery. The earliest work was done usually with heterologous blood. **Doerr** was the first, in 1910, to correlate the toxicity of normal blood with anaphylaxis. According to him, both the symptoms and post-mortem findings, after normal serum injections, correspond very closely to those of anaphylaxis. **De Kruif** did a large number of experiments on animals by withdrawing blood and reinjecting it. The blood, which is initially non-toxic, becomes toxic just prior to the appearance of coagulation. The speed of poison production corresponds to that of the production of anaphylatoxin with substances like agar. The poison production is caused by changes incidental to the clotting of the blood. **Kohler** injected a rabbit intravenously with its own previously defibrinated blood and produced acute symptoms and death. He found thrombi in the heart and large vessels, and concluded that the injected blood was toxic because of its high fibrin ferment content. **Stühmer** did experiments on the toxicity of homologous serum for rabbits and guinea-pigs. He found that this toxic condition only persists for a short time after drawing off the blood. **Schultz** found that freshly drawn homologous blood,

if applied to normal smooth muscle, produced no response until clotting set in. When that occurred, a violent contraction of the muscle resulted. From the above facts, therefore, it is evident that some change takes place in the toxicity of blood when it clots, and the toxin produced is similar to the anaphylatoxin produced by injecting agar and similar substances.

The injection of auto-blood, auto-serum after defibrination, and hetero-serum has been extensively used in the treatment of skin and other diseases. There is still much to be learned as to its exact mode of action. It is a question how much of the action of antisera used to treat diseases like diphtheria is due to the horse serum and how much to the antitoxin. **Bingel,** in 1918, treated 466 cases of diphtheria with normal horse serum, and he claims that the results were as satisfactory as in 471 controls who received antitoxic serum. **Kastenmeyer** found that animals receiving 100 times the fatal dose of diphtheria toxin were saved by injection of normal serum. **Meyer** also found that by injections of normal horse serum 33⅓ per cent. of guinea-pigs were saved after receiving a lethal dose of diphtheria bacilli, as compared with 100 per cent. saved after antitoxic serum. It is probable that, if injected early before the bacilli have had time to elaborate toxin, the injection of normal serum is successful, whereas if toxin is already formed the antiserum is better.

TECHNIQUE

Blood is withdrawn from the anticubital vein into a sterile centrifuge tube. Fifty cc. are withdrawn in children and 100 cc. in adults. The blood is shaken for 3 minutes with glass balls. It is then centrifuged thoroughly. It requires a centrifuge which makes at least 4000 revolutions a minute, and takes half an hour to separate the serum thoroughly. The serum is then drawn off and injected into the patient again, usually into the vein of the opposite arm. The quantity of serum thus obtained is about 40–45 per cent. of the original quantity of blood withdrawn. If there is difficulty in getting the serum into the vein it may be injected subcutaneously. Some have withdrawn the blood and reinjected it immediately without defibrinating, but this is difficult to do, and there is danger of embolus. The patient's own blood or the blood of another individual either healthy or suffering

from the same disease may be used. Usually 30–40 cc. of serum are injected. This treatment is repeated 2–6 times at intervals of 3–5 days.

Bronfenbrenner and **Schlesinger** think that the injections should not be given at regular intervals. They think that the blood should be withdrawn, not during the periods of freedom from symptoms when the patient's blood is probably free from circulating antigen, but immediately preceding, during, or immediately after the anaphylactic reaction. They suggest that the presence of antigen in the blood be determined either by titration of its complement or by the antitryptic index, and that the serum containing the antigen be properly preserved and be injected into patients between attacks of the disease.

DANGERS AND DISTURBANCES

Gottheil and **Satenstein** have given over 250 injections of auto-serum without any symptoms, except in 1 case. This was a bad case of gangrenous radiodermatitis in a patient with leucæmia. He had a reaction with rise of temperature after the 5th and 6th injections. This was put down to serum sickness due to sensitisation from the previous injections. **Stümpke** noted headache, rise of temperature, transient diffuse erythema or urticaria, with dyspnœa in some cases. The blood showed an eosinophilia. Epileptiform convulsions are reported by **Föckler,** and acute dilatation of the heart by **Arnold** and **Hölzel,** in cases treated with intravenous injection of antigonococcal serum.

Nicolas, Gaté, and **Dupasquier,** after auto-serum injections, record, apart from the usual leucopenia, fall in blood pressure, and diminution of blood platelets, acute pain in the lumbar region, marked evening rise of temperature, severe arthralgia, and even non-suppurative arthritis.

But on the whole there seems to be very little danger from the use of auto- or hetero-serum, provided the injections are not given at too long intervals.

EFFECT OF INJECTIONS ON THE SKIN

Spiethoff found, by the use of auto-serum and auto-blood, a change in the skin so that it showed a diminished sensitiveness

to external irritation. A case of dermatitis, which relapsed every time that tumenol zinc paste was applied, stood that application well after injections of auto-blood. Similarly, a case of psoriasis after several injections of auto-serum stood chrysarobin quite well although previously that drug reacted with intense inflammation of the skin. Reactions which had previously occurred after salvarsan injections, did not occur if the patient were previously treated with auto-serum or auto-blood injections.

THEORIES OF THE ACTION OF AUTO-SERUM, ETC.

Very little is known as to how these injections act. They seem to have a similar effect to the injection of other protein substances such as peptone, milk, etc. **Gottheil** and **Satenstein** think that it may act in some diseases by stimulating some deficiency in the endocrine glands. They tried the effect of withdrawing blood and not reinjecting but obtained no results, therefore it is not due to the blood letting, as has been suggested by **Wile** and others. **Achard** and **Flandin** think that in conditions in which sensitisation is evident the serum acquires crypto-toxic properties and can be used for purposes of desensitisation. **Praetorius** favours **Abderhalden's** suggestion that it is the injection of ferments in the serum which act on the metabolism of the tissues or through the internal secretions. The results are not due to the production of a leucocytosis, as **Spiethoff** showed that cases recovered where no leucocytosis occurred.

THE TREATMENT OF SKIN DISEASES WITH HOMOLOGOUS AUTO-SERUM, AUTO-BLOOD, AND HETERO-SERUM, AND WITH HETEROLOGOUS SERA

Psoriasis

In this disease auto-serum treatment does not have much direct effect on the eruption, but makes the lesions much more amenable to local treatment, especially with chrysarobin. **Gottheil,** and **Gottheil** and **Satenstein,** found that it cut down the time required for local treatment from weeks to days and postponed relapses for a long time. They gave a series of injections of auto-serum first, and then began vigorous local treatment with

chrysarobin. **Spiethoff, Howard Fox,** and **Fordyce** also obtained similar good results by the combined injection and local treatment. **Winfield** reports good results with auto-serum injections alone without any local treatment. **Stümpke, Trimble** and **Rothwell,** and **Schamberg** report no results from the injections.

Urticaria and Angioneurotic Œdema

Good results from auto-serum injections are reported by **Heuck, Gottheil, Achard,** and **Flandin** and **Linser. Spiethoff, Gottheil** and **Satenstein, Ullmann** and **Lux,** however, only found improvement after the injections. **Fordyce** did not have any success.

General Pruritus

Heuck, Spiethoff, Gottheil, Nicolas, Gaté, and **Dupasquier** and **Ullmann** all report good results, **Linser** records 4 cures out of 8 cases treated, and **Lux** saw benefit from the injections.

Prurigo

Spiethoff records cure after injections of inactivated auto-serum, and 5 weeks later the eruption recurred, but disappeared again on further injections. **Linser** found marked improvement with disappearance of the itching in 12 cases. **Ullmann** obtained improvement in 1 case treated. **Stümpke** also reports good results.

Dermatitis Herpetiformis

In this disease auto-serum therapy has been beneficial in the majority of cases. **Fordyce, Howard Fox, Spiethoff, Gilchrist, Schamberg,** and **Heidingsfeld** all report very good results, whilst **Heuck, Brechet, Pusey,** and **Corlett** record marked improvement. **Ullmann, Lux,** and **Fischer,** however, obtained disappointing results.

Pemphigus

Praetorius reports complete cure of a bad case of pemphigus of 2 years' duration after 1 intravenous injection of 20 cc. of non-defibrinated normal human blood. **Linser** treated 6 cases, all long-standing ones, 2 of which had mucous membrane lesions. Two cases were cured by the injections, and have remained so for

6 months. Two were so much improved that they could work. One case died of delirium tremens soon after the treatment commenced, and 1 recovered completely after 4 weeks, but relapsed 6 weeks later. A second course of injections, however, caused improvement but not a complete cure. One case of pemphigus foliaceus was improved by the injections.

Fischer treated a case of pemphigus chronicus in a girl of 20 who had had attacks off and on since childhood. She was given an injection of 20 cc. of blood from a healthy adult female. Next day the temperature was 42° C., new lesions appeared and others became like pemphigus foliaceus. Five days after the blood injections she was given 0·45 grm. neo-salvarsan intramuscularly. Next day the temperature fell to normal, and the skin lesions gradually healed up. She was discharged well 19 days after admission, and was still well 3 months later.

Heuck and **Stümpke** report improvement in cases of pemphigus after auto-serum injections, but **Gottheil** and **Satenstein** in 2 cases saw no result.

Dermatitis and Eczema

Gottheil, Spiethoff, M'Donnell, and **Lux** record good results in some cases of eczema. **Gottheil** and **Satenstein** found improvement, and **Heuck** obtained no result. **Linser** found that auto-serum injections healed most cases of infantile eczema, but in 15 cases of widespread, long-standing eczema in adults only 3 were cured by the treatment. **Ullmann** in 2 cases of generalised eczema in children obtained no results from the injections, but exceptionally good and quick results as soon as local treatment was instituted. **Treubel** found that cases of eczema with temperatures did exceptionally well on injections of auto-serum or auto-blood.

Exfoliative Dermatitis

Linser records a cure of 1 case in 4 weeks after 5 injections of auto-serum in 8 days. **M'Donnell** also reports a remarkable cure following auto-serum treatment.

Lichen Planus and other Skin Diseases

Good results are reported by **Stümpke,** but **Gottheil** found auto-serum injections ineffective.

Isolated cases of other skin conditions were treated with auto-serum by various observers. **Gottheil** found the method of some value in bad pustular acne, in furunculosis and other pus infections, but useless in leprosy and syphilis. **Lux** had no success from its use in a case of mycosis fungoides.

Skin Diseases of Pregnancy

Special mention must be made of the work done with serum injections in pregnant women. **Linser** cured a case of herpes gestationis (dermatitis herpetiformis of pregnancy) in a short time by injections of serum from healthy pregnant women. He also treated cases of other dermatoses in pregnancy, such as eczema, with the serum of healthy non-pregnant and pregnant women. He found that in the diseases which are due to a toxæmia of pregnancy (*e.g.* herpes gestationis) he did not get as good results from injections of serum of non-pregnant as from the serum of pregnant women. He thinks that the unpleasant results sometimes caused by hetero-serum treatment of non-pregnant cases are due to the use of serum of pregnant or recently delivered women.

Veirl, Stümpke, Meyer, and **Rubsamen** also report cures of cases of herpes gestationis with injections of serum of healthy pregnant women or with auto-serum. **Rongy** has recorded a good result from injections of foreign serum in the pruritus of pregnancy.

Ulcus Molle

Treubel treated 2 cases of gangrenous soft sore, the one with auto-serum and the other with auto-blood. Both cases healed rapidly without local treatment. **Mariani** found that ordinary soft sores improved with auto-serum treatment, but local treatment was required as well before the lesions healed completely.

COMPARISON BETWEEN THE DIFFERENT KINDS OF ASPECIFIC PROTEIN THERAPY

In a recent article **Mariani** gives comparative results from the use of the different forms of aspecific protein therapy. He treated 150 cases comprising 43 of skin diseases of various types, 76 of gonorrhœa with complications, and 31 of adenitis associated

with venereal ulcers. He used specific hetero-sera and hetero-vaccines, auto-serum, auto-plasma, auto-blood, aspecific hetero-sera and hetero-vaccines, and protein substances such as milk and peptone. Symptoms after a first injection were sometimes seen with hetero-sera, peptone, hetero- and auto-vaccines, but rarely with milk. Anaphylactoid reactions (8–12 days after the beginning of treatment) were fairly frequent after the use of hetero-sera, occasionally after milk, rarely after peptone and hetero-vaccines, and never after autogenous vaccines. He sometimes obtained cross reactions, *e.g.* anaphylactoid reactions occurred with milk after hetero-serum injections, with peptone after milk injections, and so on. In 1 case a marked anaphylactoid reaction occurred with an injection of egg albumin given some hours after a peptone injection. On the whole, aspecific protein therapy was found to be of very little use in dermatoses of unknown cause, and which are probably not infective, although the symptoms might be somewhat ameliorated. In pyogenic dermatoses, hetero-protein therapy had very little effect, but specific autogenous vaccines were undoubtedly advantageous.

NON-SPECIFIC VACCINE THERAPY

It is not proposed to enter into a discussion on vaccine treatment as a whole. The effect of intravenous injection of bacterial suspensions has already been considered and shown to be non-specific, the results being due to protein shock. There is still, however, to be studied the effect of giving subcutaneously or by the mouth vaccines made from the contents of the bowel in cases of alimentary anaphylaxis. This subject has been specially investigated by **Danysz**, who claims that satisfactory results can be obtained in such diseases as urticaria, eczema, psoriasis, asthma, neurasthenia, gastro-intestinal disorders, arthritis, etc. He treated his cases with saline suspensions of 4 or 5 varieties of bacteria cultivated from the stools. The vaccine is sterilised by heating for 1 hour at 70° C. The vaccine usually contained B. coli, streptococci, enterococci, diplococci, and in some cases also an anaerobe. Each cc. of vaccine contained about $\frac{1}{200}$ mgrm. of the dried bodies of the bacteria. He gave 1 cc. for the first dose, then 0·5 cc. 24 hours later, and

continued to give daily injections for a week, increasing the dose by 0·1 cc. each time up to 1 cc. He also treated cases by giving them daily the same vaccine by the mouth in doses of 1 cc. in about 150 cc. of ordinary water.

Danysz started on the theory that the albuminoid substances from the microbes in the intestine pass into the circulation and act as antigens and induce sensitisation. He claims that this occurs in all the chronic non-contagious diseases. At first he used autogenous vaccines from the bowel of each case, but later, as he found that the same bacteria occurred in the same proportions in nearly all cases, he used a polyvalent heterogenous preparation. He obtained successful results in cases of urticaria and chronic dermatitis in which the cure was permanent for some years. He also treated cases of psoriasis in which he obtained cures in 60 per cent. In some there was a recurrence in 3–6 months, but these yielded promptly when the vaccine was resumed. **Semon** has treated 7 cases of severe psoriasis by **Danysz'** method and only obtained a response in 1 case. **Barber** found that in some cases it failed completely, but admits that it is of distinct value in others.

Ersettig treated 14 syphilitics with subcutaneous injections of typhoid, paratyphoid, and cholera vaccines, giving an injection once a week. He found that the injections were capable of turning a strongly positive Wassermann reaction into a negative. They also caused a gradual modification of the syphilitic lesions, ending in their complete disappearance, even although no anti-syphilitic treatment was given. **Biach** found that injections of old tuberculin in doses of 0·01 cc. in cases of primary, secondary, and late nerve syphilis caused a marked improvement which ran parallel with the fever reaction. The injections had no effect on the Wassermann reaction.

Pus vaccines have also been used by **Nesfield** and others in the treatment of septicæmia, pneumonia, sycosis, acne, and other pyodermias. A few drops of pus are mixed with sterile water, and carbolic acid is added to sterilise the suspension. After 24 hours the suspension is injected similarly to a vaccine. I have found benefit in some cases of acne and sycosis from this method, but the results are not any better than can be obtained from ordinary vaccines.

In all infections it is a question whether treatment with non-specific vaccines is advisable. A specific vaccine may do good in infections by virtue of its containing the specific antigen and by raising the patient's resistance to that, but in non-specific therapy in general, including all the methods of non-specific desensitisation, it is doubtful whether the method is advantageous in the long run. If one believes in the theory that, in infection, part of the symptoms are due to sensitisation to the protein of the organism and part to the toxins, then removal of the sensitisation to the protein may have a harmful effect on the patient's resistance, because these sensitisation reactions are probably protective in nature. In non-infective conditions, however, such as sensitisations to some non-bacterial protein, treatment by non-specific desensitisation is a method to be recommended.

A great deal of work still requires to be done before the method of action of non-specific therapy is fully explained. In all, whether due to intravenous vaccines, peptone, milk, auto-serum, or heterologous vaccines, there is a common reaction with rise of temperature, leucocytosis, alteration in the ferments in the blood and in the permeability of the capillaries, etc. Which of these changes are essential is not decided, but there is no doubt that the parenteral administration of various albuminoid bodies causes a definite local reaction on pathological tissues which leads to their absorption. For that reason these methods have been found useful therapeutically.

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LIST OF PRINCIPAL ABBREVIATIONS

Abstr. =Abstract.

Arch. of D. and S. =Archives of Dermatology and Syphilis.

Arch. f. D. und S. =Archiv für Dermatologie und Syphilis.

A.J.M.Sc. =American Journal of the Medical Sciences.

B.M.J. =British Medical Journal.

B.J.D. and S. =British Journal of Dermatology and Syphilis.

Bull. No.—, Hyg. Lab., U.S.P.H. and M.H.S. =Bulletin No.—, Hygienic Laboratory, United States Public Health and Marine Hospital Service, Washington.

Centralblatt f. Bakt. =Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten.

C.R. Soc. Biol. =Comptes rendus des Scéances de la Société de Biologie et de ses filiales.

J.A.M.A. =The Journal of the American Medical Association.

Zeitschr. f. Immunitätsforsch. =Zeitschrift für Immunitätsforschung und experimentelle Therapie.

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